# Investigating vaccine preventable diseases and outbreaks in Australia

**A thesis submitted for the degree of Master of Philosophy Applied Epidemiology of The Australian National University**

**Alexis Pillsbury**

**May 2014**

**National Centre for Immunisation Research and Surveillance**

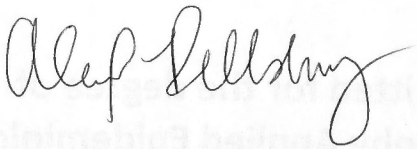
**NCEPH Supervisor**
**Dr Martyn Kirk**

**Field Supervisor**
**Dr Helen Quinn**

Australian National University

ncirs
NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

This is to certify that this thesis represents my own original work which was undertaken for the degree of Master of Philosophy Applied Epidemiology. Where investigations and/or analyses were conducted with the assistance of others, the contribution of each individual is clearly recognised and detailed within the Preface of each chapter.



Alexis Pillsbury

May 2014

# TABLE OF CONTENTS

# ABSTRACT


## Investigating vaccine preventable diseases and outbreaks in Australia

### Alexis Pillsbury BA (International Relations); MIPH; MPP

Despite having a well-established and successful National Immunisation Program (NIP), vaccine preventable diseases continue to affect communities and result in large outbreaks in Australia. Because of the dynamic nature of vaccine preventable diseases, surveillance and monitoring of epidemiological trends are necessary for informing appropriate policy development and vaccine delivery. In this thesis, I present selected works under the theme of the epidemiology of vaccine preventable diseases which I conducted while placed at the National Centre for Immunisation Research and Surveillance (NCIRS) from March 2012–2014 as a Master of Philosophy Applied Epidemiology (MAE) Scholar. The works presented comprise my MAE requirements, of which a core component is to investigate an outbreak. My first outbreak investigation was a foodborne outbreak of staphylococcal gastroenteritis at an elite athletic event, where fried rice and chicken were suspected as the cause. The remainder of my MAE work related to vaccine preventable diseases and I participated in the public health response to a state-wide outbreak of measles, including a specific investigation to determine the source of infection for a cluster of four cases infected in a paediatric hospital Emergency Department (ED). I developed an algorithm for this contact tracing investigation, although the source of infection was never identified. Measles was also the subject of my applied epidemiological project, where I considered characteristics of measles in the post-elimination era with an emphasis on the role of healthcare setting transmissions in perpetuating outbreaks. In the 2012 outbreak, 16 individuals

infected with measles transmitted the illness to 36 others in EDs and General Practice (GP) clinics. In addition, I examined the vaccine effectiveness of the measles vaccine that may allow outbreaks to persist in a setting of high vaccine coverage. I analysed pertussis trends in Australia from 2006–2012, which revealed that the average annual notification rate was more than 2.8 times that of the previous decade with a significant change in the pattern of age-specific incidence. The steepest increases in notification rates were among children less than 10 years, especially those 2–4 years and 6–9 years of age. Reasons for this shift include increased diagnostic testing and more rapid waning of effectiveness post vaccination with acellular vaccines compared to whole cell vaccines used in previous decades. The shift was exacerbated by cessation of the 18 month dose in the National Immunisation Program (NIP) from 2003. Lastly, I evaluated Australia's post-marketing surveillance for intussusception (IS) following the introduction of the rotavirus vaccines in 2007. The evaluation found that despite not having planned surveillance, Australian systems evolved to include several surveillance components that were more effective than the nation's passive adverse event following immunisation (AEFI) surveillance system at detecting cases and assessing causality. The work in this thesis contributed to the work of NCIRS and improves our understanding of the epidemiology of vaccine preventable diseases in Australia.

# ACKNOWLEDGEMENTS

There are many people I would like to thank for making my MAE experience a success. First and foremost, I am grateful to NCIRS, and specifically to Professor Peter McIntyre, for providing me with a field placement and access to fantastic colleagues and mentors as well as an inspiring learning environment.

I could not have completed my MAE without my two primary supervisors, Dr Helen Quinn of NCIRS and Dr Martyn Kirk of the National Centre for Epidemiology and Population Health (NCEPH). Helen spent countless hours with me helping me to develop my data analysis skills. Her patience never wavered no matter how many times I required clarification of how to assess birth cohorts in regards to the vaccination schedule. I couldn't have asked for a more supportive, encouraging supervisor or skilled mentor. As my academic supervisor, Martyn provided me with guidance, epidemiological instruction, endless feedback on my work and its direction. I am appreciative of the honest and constructive feedback that Martyn always delivered; my work is better for it.

I would also like to thank Dr Vicky Sheppeard, formerly of the Western Sydney Public Health Unit (PHU), who offered me the opportunity to assist with several public health outbreak response efforts. Vicky acted as an extremely supportive mentor over the course of my MAE experience. My MAE would not have been as rich a learning experience without the opportunities Vicky offered me.

Additionally, I would like to thank NCEPH staff, including Dr Stephanie Davis, who along with Martyn, taught the majority of the MAE intensive courses. I benefited immensely from them. I am also appreciative of the teaching sessions provided to my small MAE cohort by Dr Mahomed Patel, who taught us a whole different way of approaching learning and thinking about all things epidemiological and otherwise. I hope I have become a better academic and epidemiologist because of his lessons

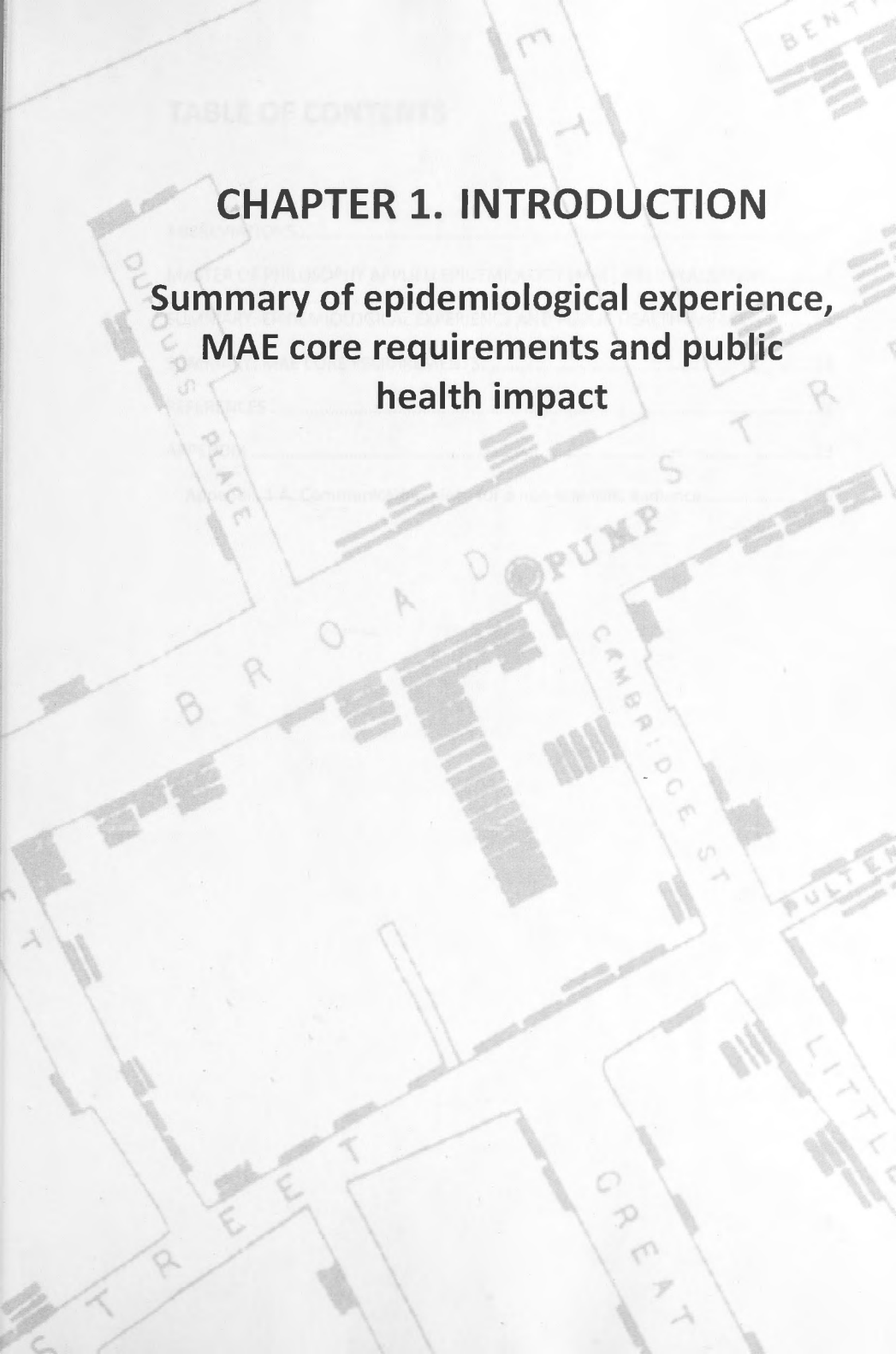
which I won't soon forget.

I would also like to express my gratitude to the members of the 2012 MAE cohort, specifically the three other full time MAEs: Ms Rowena Boyd, Ms May Chiew and Dr Ee Laine Tay. I appreciate their consistent support and how much I learned from each, but in particular May, who was my epidemiology partner in work and study for the entirety of the two year program.

Finally, I would like to acknowledge my family and thank them for their support and patience during this undertaking.

# CHAPTER 1. INTRODUCTION

## Summary of epidemiological experience, MAE core requirements and public health impact



# TABLE OF CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| **ACSOV** | Advisory Committee on the Safety of Vaccines |
| **AEFI** | Adverse Event Following Immunisation |
| **ASID** | Australasian Society for Infectious Diseases |
| **ATAGI** | Australian Technical Advisory Group on Immunisation |
| **CDC** | Communicable Disease Control (Conference) |
| **CDI** | *Communicable Diseases Intelligence* (Journal) |
| **CDNA** | Communicable Disease Network Australia |
| **CHW** | The Children's Hospital at Westmead |
| **DOH** | Department of Health |
| **DOHA** | Department of Health & Ageing |
| **ED** | Emergency Department |
| **FETP** | Field Epidemiology Training Program |
| **ICPMR** | Institute for Clinical Pathology & Medical Research |
| **IgE** | Immunoglobulin E |
| **MAE** | Master of Philosophy Applied Epidemiology |
| **MIPH** | Master of International Public Health |
| **NCEPH** | National Centre for Epidemiology & Population Health |
| **NCIRS** | National Centre for Immunisation Research & Surveillance |
| **NIP** | National Immunisation Program |

| | |
|---|---|
| **NSW** | New South Wales |
| **PEP** | Post-Exposure Prophylaxis |
| **PHU** | Public Health Unit |
| **TGA** | Therapeutic Goods Administration |
| **TEPHINET** | Training Programs in Epidemiology & Public Health Interventions Network |

# MASTER OF PHILOSOPHY APPLIED EPIDEMIOLOGY (MAE) FIELD PLACEMENT

## Introduction

I became aware of the Master of Applied Epidemiology (MAE) program at the time the program was undergoing evaluation and being re-designed. Having completed postgraduate studies in public policy, and then international public health, I was slowly but surely narrowing in on my area of interest. The Master of International Public Health (MIPH) had piqued my curiosity in epidemiology and Australia's Field Epidemiology Training Program (FETP) was exactly the type of hands on education I was after. I was both excited and grateful to be accepted as part of the first cohort in the restructured Master of Philosophy Applied Epidemiology in 2012.

My field placement commenced in March 2012 at the National Centre for Immunisation Research and Surveillance (NCIRS) located in New South Wales (NSW) at the Kids Research Institute within the Children's Hospital at Westmead (CHW). It was an ideal placement. My previous studies were social science and policy focussed; NCIRS, while incorporating aspects of these areas, relies heavily on quantitative research, at the time an area of relative inexperience for me. I had long wished to participate in the meshing of epidemiological research and policy; placement at NCIRS offered me that opportunity.

My primary field supervisor was Dr Helen Quinn, an epidemiologist and Research Fellow within the NCIRS Surveillance Unit. Dr Quinn, a 2005 graduate of the MAE program, holds a conjoint academic appointment as Lecturer in the Discipline of Paediatrics and Child Health and the School of Public Health, University of Sydney. During my time at NCIRS, Director Peter McIntyre also provided supervision.

## About NCIRS

Stemming from the 1993 National Immunisation Strategy, the Australian

Government Department of Health and Ageing*(DOHA) established the Immunise Australia Program in 1997 with its Seven Point Plan stressing the need for education and research. The Plan specifically called for the establishment of NCIRS to 'coordinate and conduct research and analysis of epidemiological and sociological aspects of immunisation and vaccine preventable diseases (VPDs) and provide policy information and advice to inform future directions for the national childhood immunisation program'.[1]

NCIRS was established at the CHW where it now remains as a component of the CHW's Kids Research Institute infectious disease and immunology research stream. NCIRS also has academic affiliation with the University of Sydney's Department of Paediatrics and Child Health and School of Public Health, and simultaneously maintains an array of government and academic collaborations at state, national and international levels. Operationally, NCIRS is currently divided into two sections: Clinical Research; and Policy and Surveillance. The latter is funded primarily by NCIRS's main partners: the Department of Health (DOH); the NSW Ministry of Health; and the CHW. Clinical Research, however, is supported by a mixture of competitive grants and industry supplied funding; details of all clinical research funding received are publicly available. Both an Advisory Board and a Scientific Advisory Committee exist to govern and oversee NCIRS activities and operations.

*Note: Some work conducted or referred to in this thesis occurred prior to the Commonwealth Department of Health and Ageing becoming the Department of Health. Consequently, "Department of Health and Ageing" and "DOHA" are used when referencing past work.

Within the main operational sections, ten project groups function:

- Evidence Based Practice and Policy Support
- Clinical Research (including trials)
- Surveillance (including the Australian Childhood Immunisation Register)
- Adverse Events
- Indigenous/Migrant Health
- Communications and Education
- Social Research
- Serosurveillance
- Dataset/Technology Management
- Library and Information Management Committee[2]

Broadly, NCIRS conducts research targeted at reducing the incidence of vaccine preventable diseases and increasing the uptake of vaccinations recommended by the National Immunisation Program (NIP). NCIRS also advises on vaccinations and VPDs, including providing information for the Australian Immunisation Handbook, the source of Australia's immunisation clinical guidelines.[3] NCIRS informs and offers recommendations to government immunisation policy in conjunction with the Australian Technical Advisory Group on Immunisation (ATAGI). Moreover, NCIRS contributes to surveillance planning and policy, and also trains and supervises a range of postgraduate students.[4]

Understandably, the responsibilities, roles and staff numbers at NCIRS have expanded and evolved in line with the increased number of vaccinations and targeted age groups recommended by the NIP. In the early 1990s the NIP's recommended childhood vaccination schedule included diphtheria, tetanus, pertussis, polio, measles, mumps and rubella. It has since expanded to incorporate hepatitis B, *Haemophilus influenzae* type b (Hib), pneumococcal, rotavirus, meningococcal C, varicella, human papillomavirus (HPV) and influenza.[5]

# SUMMARY: EPIDEMIOLOGICAL EXPERIENCE AND PUBLIC HEALTH IMPACT

My MAE experience kicked off with a bang. After completing my first MAE residential course block, I began my field placement at NCIRS. But immediately before even having time to learn my NCIRS's colleagues' names, Western Sydney Public Health Unit's (PHU) Parramatta office offered me the opportunity to become involved with the public health response to what was to become NSW's largest measles outbreak since 1998. It was fortuitous, for my subsequent involvement .provided the foundation for the majority of my MAE learning.

The outbreak's index case had infected several others before being diagnosed; consequently the contact tracing effort was sizable. After receiving a crash course in measles epidemiology, I was immediately entrusted to trace and call contacts, and then to provide appropriate information and advice. As the outbreak grew, I later assisted in organising and executing multiple post-exposure prophylaxis (PEP) clinics at the CHW for those exposed to subsequent measles cases.

In addition to this initial assistance, I also participated in the ongoing monitoring of the outbreak via daily teleconferences led by Dr Vicky Sheppeard, then Manager of the Western Sydney Nepean and Blue Mountains PHU. It was a valuable experience, offering me insight into the 'real-time' monitoring and management of a disease outbreak. Additionally—as part of an investigation into the source of infection for a cluster of cases in the outbreak, a task I undertook jointly with my MAE and NCIRS colleague Ms May Chiew—I accompanied Dr Sheppeard as she met staff from the Emergency Departments (EDs) where several cases had been exposed. Attempting to trace transmission lines and account for the source of infection for as many cases as possible is critical to stopping an outbreak and for Australia to remain on track for ratifying measles elimination status.

The outbreak provided me with numerous other public health experiences. At the local level, I along with Ms Chiew and the public health registrar working at the

Western Sydney PHU at the time delivered a presentation to the NCIRS Journal Club and to the CHW Infectious Disease Meeting regarding the outbreak's initial stages, its affected demographics, and its contributing factors. I also participated in the debrief convened by Dr Sheppeard with local public health officers, assessing the response effort's successes, challenges and limitations.

By September, the outbreak had spread beyond Western Sydney. The response effort was now being overseen by the NSW Ministry of Health, and I was requested by the Communicable Disease Branch to assist. It was a fine opportunity; I could now observe the response effort from a state-wide perspective.

Of my roles with the Ministry, conducting analysis of measles exposure in healthcare settings—in particular, overlap times between primary and secondary cases—was key. Existing policy employed a two hour contact tracing rule; due to the ability of the measles virus to remain airborne for up to two hours, PHUs were instructed to contact trace all potential contacts entering a location within two hours of an infected case departing it. My analysis, however, demonstrated a need to reassess this policy. Using data from both Western Sydney and Sydney South Western PHUs, I found that in this particular outbreak all known secondary cases who acquired measles in a healthcare setting had in fact overlapped in time and place with their source case. Consequently, I drafted a brief for the NSW Measles Expert Working Group summarising these findings. In this era when measles cases are rare, resources may be better spent contact tracing only those who were known to have overlapped closely in time with a source case rather than adhering to the two hour rule.

At the outbreak's end, I subsequently performed more extensive analysis incorporating all outbreak cases infected in a healthcare setting. This work was conducted collaboratively with colleagues from Western Sydney and Sydney South Western PHUs and NCIRS. In March 2013, I delivered a presentation regarding this analysis at the joint Communicable Disease Control (CDC) and Australasian Society for Infectious Diseases (ASID) Conference in Canberra. This also resulted in a draft manuscript to be submitted for publication.

My experience with the measles outbreak inspired me to conduct a vaccine effectiveness analysis for both the outbreak cohort and at the population level for notifications 2006–2012. Though the outbreak had clearly been fuelled by failure to vaccinate, and not vaccine failure, vaccine effectiveness analyses are nonetheless important components of evaluating the vaccination schedule and maintaining public and provider confidence in vaccines. Moreover, such analyses highlight the true culprit in an outbreak: vaccination coverage gaps and vulnerable demographics. This was the final project I conducted for my MAE. Given how much of my two year MAE experience was spent focused on measles, and given my field placement at NCIRS, this was an extremely appropriate culmination to my MAE. This work was provided to the NSW Ministry of Health as well as to the Measles Elimination Working Party and the Measles Verification Committee.

Though measles occupied a significant proportion of my MAE time, other projects involved different diseases, primarily vaccine preventable. As NCIRS is required by its contract with the DOH to undertake periodic reviews of all vaccine preventable diseases, I was tasked with conducting an updated epidemiological review of pertussis trends in Australia for the period 2006–2012. The final report will be submitted to the DOH, the Communicable Diseases Network Australia (CDNA) and the Australian Technical Advisory Group on Immunisation (ATAGI) and will be published in *Communicable Diseases Intelligence* (CDI). Parts of this report have also been used by the Pertussis Working Party in the Party's final advice to inform re-instatement of the 18 month booster dose which was removed from the immunisation schedule in 2003.

Additionally, I evaluated Australia's adverse event following immunisation (AEFI) surveillance of intussusception (IS) associated with the introduction of the rotavirus vaccines in the mid-2000s. This was not a typical disease surveillance system evaluation. IS surveillance was not planned or centrally managed. Efforts were somewhat organic in nature, relying on contributions from several existing surveillance systems. NCIRS—in line with the 2011 Horvath Review into the management of adverse events associated with Panvax and Fluvax, which

recommended a strengthening of Australian AEFI surveillance efforts[6]–views novel surveillance efforts, such as those comprising of more than one surveillance mechanism, as key to future vaccine safety surveillance. However, no assessments of these 'ad hoc' surveillance efforts had yet been made. I hoped this first evaluation would, ideally, inform and assist future surveillance efforts that utilise multiple surveillance mechanisms to achieve a singular surveillance goal. My preliminary results were presented at the 7th Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) Bi-regional Scientific Conference in Danang, Vietnam, in November 2013. The evaluation report will be provided to the DOH, the Therapeutic Goods Administration (TGA) and the Advisory Committee on the Safety of Vaccines (ACSOV).

Finally, as an exception to all my VPD work, I was invited to investigate a foodborne gastroenteritis outbreak on behalf of the Western Sydney PHU in June 2012. This outbreak affected more than 20 individuals who had eaten dinner at a commercially catered buffet served at a large elite sporting event. Though an exact food exposure could not be identified, laboratory tests of faecal samples were positive for *Staphylococcal aureus*. Despite being a significant contributor to foodborne illness in Australia, little is published on *Staphylococcal aureus* or staphylococcal food poisoning (SFP). Consequently, I wrote a report about this investigation, co-authored with Ms Chiew, Dr Sheppeard and Mr John Bates of Queensland Health Forensic and Scientific Services; the manuscript was published in June 2013 by CDI.

Lastly, with NCIRS being favourably situated between the CHW and Westmead Hospital, I was able to attend many educational sessions at both. I also spent two days visiting the Institute for Clinical Pathology and Medical Research (ICPMR) at Westmead Hospital to learn about the services and research conducted there with a view to better understanding the relationship between laboratory testing and epidemiology.

I feel extremely fortunate to have been able to develop my analytical and quantitative skills at a well-respected and influential national research centre. The learning opportunities at NCIRS were second to none. My MAE experience was

greatly enhanced, however, by being offered several hands-on public health experiences by the Western Sydney PHU which services one of Australia's most diverse populations. The unique combination of opportunities I was afforded impressed upon me the various applications of field epidemiology.

# SUMMARY: MAE CORE REQUIREMENTS

The following list summarises the MAE core requirements and the specific projects contributing to the fulfilment of each requirement.

## Outbreak investigation

- An outbreak of staphylococcal food poisoning in a commercially catered buffet **(Chapter 2)**
- Tracing lines of transmission in a measles outbreak, Western Sydney, New South Wales, 2012 **(Chapter 3)**

## Evaluation of a public health surveillance system

- Australian post-licensure surveillance for intussusception associated with receipt of rotavirus vaccines **(Chapter 6)**

## Analysis of public health data

- Australian vaccine preventable disease review series: pertussis 2006–2012 **(Chapter 5)**
- An outbreak of staphylococcal food poisoning in a commercially catered buffet **(Chapter 2)**
- An assessment of measles vaccine effectiveness, Australia, 2006–2012 **(Chapter 4)**
- The changing epidemiology of measles in an era of elimination: lessons from healthcare setting transmissions of measles during an outbreak in Australia, 2012 **(Chapter 4)**

## Design and execution of an epidemiological study

- An assessment of measles vaccine effectiveness, Australia, 2006–2012 **(Chapter 4)**
- The changing epidemiology of measles in an era of elimination: lessons from healthcare setting transmissions of measles during an outbreak in Australia, 2012 **(Chapter 4)**
- An outbreak of staphylococcal food poisoning in a commercially catered buffet **(Chapter 2)**
- Tracing lines of transmission in a measles outbreak, Western Sydney, New South Wales, 2012 **(Chapter 3)**

## Teaching experience

- Lessons from the Field session ('Money matters: a brief introduction to health economic evaluation and cost effectiveness assessments in publicly funding vaccines in Australia') designed and taught to four MAE colleagues **(Chapter 7)**
- Epi Info™ 7 training session designed and taught with four MAE colleagues as part of the CDC Pre-Conference Workshop session (March 2013) **(Chapter 7)**
- Assisted teaching sessions of the National Centre for Epidemiology and Population Health (NCEPH) Outbreak Investigation course to the 2013 MAE cohort

## Submission of manuscript for publication in peer-reviewed journal

- Pillsbury A, Chiew M, Bates J, Sheppeard V. An outbreak of staphylococcal food poisoning at a commercially catered buffet. Communicable Diseases Intelligence. 2013; 37(2): E144-148. **(Chapter 2)**
- Pillsbury A, Quinn H, McIntyre P. Australian vaccine preventable disease review series: pertussis 2006–2012. (Submitted to CDI; publication pending) **(Chapter 5)**
- The changing epidemiology of measles in an era of elimination: lessons from healthcare setting transmissions of measles during an outbreak in Australia, 2012 (late stage draft; to be submitted to Western Pacific Surveillance and Response) **(Chapter 4)**

## Oral conference presentation

- 'The clinical setting is important for measles transmission: lessons from the 2012 NSW outbreak', Joint CDC and ASID Conference, Canberra, March 2013 **(Chapter 4, Appendix)**
- 'Re-thinking traditional adverse event following immunisation (AEFI) surveillance: lessons from Australia's successful experience with intussusception (IS) surveillance following the 2007 introduction of rotavirus vaccines', 7th TEPHINET Bi-regional Scientific Conference, Danang, Vietnam, November 2013 **(Chapter 6, Appendix)**

## Drafting of public health communication aimed at a non-scientific audience

- Updating the 'Vaccines, allergy & asthma' factsheet which is one of a series of NCIRS factsheets available for immunisation providers and members of the public. This version will ultimately replace the version currently appearing on the NCIRS website. **(Chapter 1, Appendix)**

## Literature review

- Extensive literature reviews were conducted for all project chapters **(Chapters 2–6)**.

## Completion of MAE courses

- I attended all MAE course blocks, presented all required Field Reports and participated in all Problems from the Field sessions. I successfully completed all required MAE academic courses:

  -Outbreak Investigation

  -Public Health Surveillance

  -Analysis of Public Health Data

  -Methods in Applied Epidemiological Research

  -Issues in Applied Epidemiology

**Table 1.1. Summary of MAE core requirements included within the chapters of this thesis**

| | Literature review | Data analysis | Outbreak investigation | Surveillance system evaluation | Epidemiological project | Peer reviewed publication | Oral presentation | Communication for non-scientific audience | Teaching experience |
|---|---|---|---|---|---|---|---|---|---|
| **Chapter 1**: Introduction | | | | | | | | ✓ | |
| **Chapter 2**: Outbreak investigation, S. aureus | ✓ | ✓ | ✓ | | ✓ | ✓ | | | |
| **Chapter 3**: Outbreak investigation, measles | ✓ | | ✓ | | ✓ | | | | |
| **Chapter 4:** Epidemiological project | ✓ | ✓ | | | ✓ | ✓* | ✓ | | |
| **Chapter 5:** Data analysis | ✓ | ✓ | | | | ✓* | | | |
| **Chapter 6:** Surveillance system evaluation | ✓ | | | ✓ | | | ✓ | | |
| **Chapter 7:** Teaching | | | | | | | | | ✓ |

*Submitted or to be submitted for publication.

# REFERENCES

1. Australian Government Department of Health. Immunise Australia Program. [cited 2012 March]; Available from: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/history-of-ia-prog.

2. National Centre for Immunisation Research and Surveillance (NCIRS). Orientation information: welcome to the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases. Sydney 2012.

3. National Centre for Immunisation Research and Surveillance (NCIRS). Australian immunisation handbook. 2012

4. National Centre for Immunisation Research and Surveillance (NCIRS). About us. 2012 [cited 2012 March]; Available from: http://www.ncirs.edu.au/about/index.php.

5. Macartney K. Principles behind the immunisation schedule. Canberra 2011.

6. Australian Government Department of Health and Ageing. Review of the management of adverse events associated with Panvax and Fluvax. Canberra 2011.

# APPENDIX

## Appendix 1.A. Communication piece for a non-scientific audience

FactSheet

ncirs
NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

# Vaccines, allergy & asthma

- Asthma and allergic disease rates have increased in the past few decades though the cause of these increases remains unknown.
- The 'hygiene hypothesis' has postulated that due to increased sanitation and hygiene children's immune systems are not primed in the way they used to be to fight pathogens.
- While much research remains inconclusive, several large epidemiological studies have found that there is no increased risk of allergy with vaccination.

Asthma and allergic disease rates have increased dramatically in the last few decades. The exact reasons for this remain unknown. It has been postulated, however, that vaccines may stimulate some type of change in the immune system which may affect the development of chronic allergic and autoimmune conditions.

### What is the proposed association between vaccines and allergy?

Back in the 1980s and 1990s, several researchers presented findings based on their observations that families with many children or children who attended day-care had lower rates of hay fever and eczema.[1] Another study demonstrated that children who first attended day-care at an older age experienced an increased prevalence of allergy compared with children who first attended at a younger age.[2] These studies were interpreted to mean that because children tend to pass infections around and therefore increased exposure to infectious pathogens—or unhygienic conditions—protected children from allergies. This became known as the 'hygiene hypothesis'.[1] The hygiene hypothesis led to the suggestion that vaccines, because they prevent infections, may indirectly cause allergy.[3] Consequently, supporters theorised, increasing use of vaccination and decreasing rates of disease have led to an increase in allergy rates.

### Is the hygiene hypothesis biologically plausible?

The idea is that childhood infections train the immune system to launch an effective defence against foreign pathogens. With improved hygiene and sanitation, the hygiene hypothesis suggested that this training has been lost, allowing for an imbalanced immune response. Consequently, when allergens are detected, the immune system overreacts triggering an allergic reaction.

Those who have allergies have an exaggerated immune response which results in the increased production of allergen-specific immunoglobulin E (IgE). Allergens are inhaled, processed and presented to helper T cells. There are two types of helper T cells: one which facilitates the production of allergen-specific IgE (Th2) and one which decreases the production of IgE (Th1). Th2-type responses dominate at birth but early childhood infections trigger Th1-type responses. Therefore the hygiene hypothesis postulates that a delay in childhood infections allows Th2-type responses to dominate and persist and thus the risk of allergic diseases increases. Because vaccines prevent these infections, it is suggested that vaccines might similarly result in increased risk of allergy.[4]

### What does the evidence suggest about the relationships between vaccines and allergy?

Firstly, the hygiene hypothesis argument has been controversial. Some studies seem to support it while others find it flawed.[5,6,7] Reasons it may be flawed include the fact that most common childhood infections are not vaccine preventable. Moreover, childhood illnesses which are prevented by vaccination are typically those that are most infectious, like measles and pertussis. These are highly contagious and easily transmitted in settings irrespective of hygiene or environment. Also, Th2-type responses are triggered by worm and helminth infections –as opposed to Th1-type responses which are triggered by viruses and bacteria. Children with high worm/helminth infection rates, however, have been observed to have lower incidence of allergies compared with other children.[8]

Irrespective of the hygiene hypothesis, however, many large epidemiological studies have concluded that there is no evidence of an increased risk of allergic diseases associated with vaccination. Moreover, recent epidemiological studies do not support the idea that children who have not been vaccinated against infectious diseases have had less allergy or asthma than those children who have received recommended vaccinations.[9]

In terms of specific vaccines, the *Bacillus Calmette-Guerin* or BCG vaccine (tuberculosis vaccine) has been the most studied of any vaccine in regards to risk of allergy; no studies have found an increased risk.[9]

Several early studies of the pertussis vaccine reported increased asthma diagnoses among those who had been vaccinated compared with those who had not received the vaccine.[10,11] These earlier studies were not as robust as later, larger and more controlled studies which have concluded no association between the pertussis vaccine and allergy.[12,13,14]

Studies of the measles-mumps-rubella (MMR) vaccine have found no link between vaccine and allergy.[12,13] Similarly, no study has demonstrated an association between poliomyelitis vaccine and increased prevalence of allergic illness. Most studies have also concluded no increase associated with *Haemophilus influenzae* type b (Hib) vaccine. Two Hib studies demonstrated a small but significant increase in prevalence of asthma[13,15]; one of these studies, however, acknowledged their findings could have been influenced by methodological problems.

Because research used to understand whether or not vaccination is associated with increased prevalence of allergy/asthma has been conducted using differing methodologies and study populations, and because there is still much that is not well understood regarding allergy and the immune system, it is difficult to confidently confirm or deny the connection between vaccines and allergy. To date, however, there is no evidence of increased risk of allergy or asthma associated with vaccination.[9]

## References


1. Strachan D. Hay fever, hygiene, and household size. *BMJ* 1989;299: 1259–1260.

2. Kramer U, Heinrich J, Wjst M, Wichmann HE. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999; 353(9151): 450-454.

3. Odent MR, Culpin EE, Kimmel T. Pertussis vaccination and asthma: is there a link? *JAMA*. 1994;272: 592–593.

4. Kay AB. Allergy and allergic diseases. *N Engl J Med*. 2001; 344: 30–37.

5. Ball TM, Castro-Rodriguez JA, Griffith KA, et al. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000; 343: 538–5436.

6. Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol* 2001; 1(1): 69-75.

7. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science*. 2002; 296: 490–494.

8. van den Biggelaar AH, van Ree R, Rodrigues LV, et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite induced interleukin-10. *Lancet* 2000; 356: 1723–1727.

9. Sanchez-Solis M, Garcia-Marcos L. Do vaccines modify the prevalence of asthma and allergies? *Expert Rev Vaccines* 2006; 5(5): 631-640.

10. Kemp T, Pearce N, Fitzharris P et al. Is infant immunization a risk factor for childhood asthma or allergy? *Epidemiology* 1997; 8(6): 678-680.

11. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax* 1998; 53(11): 927-932.

12. Anderson HR, Poloniceki JD, Strachan DP, Beasley R, Bjorsten B, Asher MI, ISAAC Phase I study group. Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. *Am J Public Health* 2001; 91(7): 1126-1129.

13. DeStefano F, Gu D, Kramarz P et al. Vaccine safety datalink research group childhood vaccinations and risk of asthma. *Pediatr Infect Dis J* 2002; 21(6): 498-504.

14. Bersen RMD, de Jongste JC, van der Wouden JC. Lower risk of atopic disorders in whole cell pertussis-vaccinated children.. *Eur Respir J* 2003; 22(6): 962-964.

15. Laubereau B, Grote V, Holscher G et al. Vaccination against *Haemophilus influenza* type b and atopy in east German schoolchildren. *Eur J Med Res* 2002; 7(9): 387-392.

16. Offit P & Hackett C. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics* 2003; 111(3): 653-659.

17. Greenwood V. Why are asthma rates soaring? *Scientific American* April 14, 2011.

# CHAPTER 2. OUTBREAK INVESTIGATION

## An outbreak of staphylococcal food poisoning in a commercially catered buffet

# TABLE OF CONTENTS

# PREFACE

## Background and scope of the chapter

Between January 2000 and March 2012, 14 staphylococcal food poisoning (SFP) outbreaks were recorded by OzFoodNet, affecting more than 400 individuals. Despite being a common cause of foodborne illness worldwide, little is published on SFP in Australia.

On 2 June 2012, a SFP outbreak occurred at a commercially catered elite sporting event in Sydney. My Master of Philosophy Applied Epidemiology (MAE) and National Centre for Immunisation Research and Surveillance (NCIRS) colleague Ms May Chiew and I were assigned to the Western Sydney Public Health Unit (PHU) to lead the epidemiological component of the outbreak investigation.

This chapter details the ensuing epidemiological and microbiological investigations.

## Investigatory role

The initial notification of the gastroenteritis outbreak was received by the Western Sydney PHU over the weekend of 2 June. PHU staff on call conducted several preliminary interviews with ill individuals and obtained a list of foods served by the caterers. Based on the timing and severity of symptoms, senior PHU members believed the infection likely occurred the same day as the outbreak, probably during the dinner service. Following this advice, Ms Chiew and I assumed responsibility for the outbreak investigation on Monday morning. We drafted a food exposure questionnaire based on the food list obtained by PHU staff and interviewed the 36 individuals who comprised the dining cohort of interest (Appendix 2.A). In order to inform the direction of our outbreak investigation and for the purposes of updating all those with a vested interest, we liaised with members of the affected sporting organisation, New South Wales (NSW) Ambulance, NSW Food Authority, the hospitals where severely affected individuals had been transported, and Queensland Health Forensic and Scientific

Services where faecal samples had been sent. We conducted all analysis, followed up on the microbiological investigation and drafted the final outbreak report in collaboration with Dr Vicky Sheppeard of the Western Sydney PHU and Mr John Bates of Queensland Health Forensic and Scientific Services.

All interviews, analysis, communication with the various parties involved, and drafting of the manuscript were conducted equally by Ms Chiew and me. As first author on the manuscript, I assumed responsibility for submitting the publication, replying to reviewers' comments and finalising the manuscript. The manuscript was published in *Communicable Diseases Intelligence* (CDI) in June 2013 (Vol. 37, No. 2) and is included in this chapter.

## Lessons learned

This outbreak investigation gave me the opportunity to apply the lessons learned during the MAE outbreak investigation course. The course had provided a solid foundation, arming me with a framework for approaching outbreak investigation. Nonetheless, the practical application of the theory, of actually conducting an investigation on the ground and in 'real time', proved a much different experience.

This was my first time collecting, organising and analysing my own data. It impressed upon me that having a thorough, clear questionnaire and clean data entry are critical to an investigation's efficiency. With respect to the analysis, I learned a useful lesson regarding what to do when presented with '0 cells' in the exposure-outcome two-by-two table. In this outbreak, there were no ill people who did not eat either chicken stir-fry or fried rice. Calculating risk ratios and stratifying were both consequently impossible. Because we were unable to calculate risk ratios for chicken stir-fry and fried rice, we could not simply state that one of these two foods was the likely cause of the outbreak because we had a high risk ratio. We knew, however, that although the risk ratios for these two foods remained undefined, each yielded a significant p-value. No other food exposure yielded a high risk ratio; none was statistically significant. Moreover, we could calculate risk difference to demonstrate a strong association

between both chicken stir-fry and fried rice and illness. From our understanding of staphylococcal food poisoning, both chicken stir-fry and fried rice were plausible causes of illness. The fact that 20 out of 22 cases ate both chicken stir-fry and fried rice made it impossible to determine whether one exposure was singularly responsible for the outbreak. Cross-contamination was also a possibility.

Leading the epidemiological component of this investigation exposed me to another challenge: working across the various sectors involved in a foodborne outbreak. Public health authorities and regulators may not always view investigation outcomes and response efforts in the same way. Negotiating across sectors was an eye-opening lesson in patience and diplomacy.

## Public health impact

Heymann states that approximately 25% of healthy individuals are carriers of *Staphylococcus aureus*.[1] Because of this high carriage rate, strategies responding to and preventing *S. aureus* outbreaks generally do not target carriage; instead transmission prevention is sought via appropriate food handling techniques. But while food handling guidelines exist, in practice the degree of their enforcement is unknowable. Outbreaks such as this, however, provide valuable opportunities to reinforce appropriate food handling. Moreover, investigating and reporting on outbreaks—especially those highlighted by media as this one was—are necessary public health responsibilities and confidence-building measures.

Though *S. aureus* is a common cause of foodborne illness, outbreaks are frequently underreported. For this reason, contributing investigation reports to the existing evidence base is important. Our investigation report was published in CDI and the results were presented by Dr Sheppeard to the CHW Infectious Disease Meeting.

## Acknowledgements

I was fortunate to have been entrusted with this outbreak investigation by the

Western Sydney PHU, and, in particular, by Dr Vicky Sheppeard. The MAE requirement for participating in an outbreak investigation was not one I could fulfil at NCIRS. However, Dr Sheppeard welcomed me at the PHU. She proved an excellent mentor, and the opportunity to learn from PHU colleagues was a beneficial supplement to my NCIRS field placement.

Indispensable to the investigation, Mr John Bates at the Queensland Health Forensic and Scientific Services not only conducted toxin tests on specimens, but also explained the testing and results to me and Ms Chiew. Mr Timothy Sloan-Gardner of OzFoodNet assisted by compiling all *S. aureus* outbreak data since 2000 into a report.

Both NCIRS and Australian National University (ANU) supervisors—as well as Dr Sheppeard and Mr Bates—patiently reviewed and edited the draft. Ms Jennie Musto of the NSW Ministry of Health also provided feedback on the report. Finally, ANU supervisors Drs Martyn Kirk and Stephanie Davis were helpful in providing guidance regarding our actions and analysis during the outbreak.

# ABBREVIATIONS

| | |
|---|---|
| **ANU** | Australian National University |
| **AR** | Attack Rate |
| **CDI** | *Communicable Diseases Intelligence* (Journal) |
| **CHW** | The Children's Hospital at Westmead |
| **ED** | Emergency Department |
| **MAE** | Master of Philosophy Applied Epidemiology |
| **NCIRS** | National Centre for Immunisation Research & Surveillance |
| **NSW** | New South Wales |
| **PHU** | Public Health Unit |
| **SFP** | Staphylococcal Food Poisoning |
| **VPD** | Vaccine Preventable Disease |

# AN OUTBREAK OF STAPHYLOCOCCAL FOOD POISONING IN A COMMERCIALLY CATERED BUFFET

**Ms Alexis Pillsbury**[1,2], Master of Philosophy (Applied Epidemiology) Scholar

Ms May Chiew[1,2], Master of Philosophy (Applied Epidemiology) Scholar

Mr John Bates[3], Chief Scientist

Dr Vicky Sheppeard[4], Medical Officer, Population Health

**Affiliation(s)**

1. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), The Children's Hospital at Westmead and the University of Sydney, New South Wales, Australia.
2. National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australia.
3. Public Health Microbiology, Queensland Health Forensic and Scientific Services, Queensland Health, Archerfield, Queensland, Australia.
4. Nepean Blue Mountains and Western Sydney Public Health Unit.

**Published in *Communicable Diseases Intelligence*, June 2013, Vol. 37, No. 2**

# An outbreak of staphylococcal food poisoning in a commercially catered buffet

Alexis Pillsbury, May Chiew, John Bates, Vicky Sheppeard

## Abstract

Staphylococcal food poisoning is a common cause of foodborne illness. In Australia, since 2000, approximately 30% of foodborne *Staphylococcus aureus* outbreaks reported to OzFoodNet have been associated with foods prepared by commercial caterers. We conducted a retrospective cohort analysis of an outbreak of gastrointestinal illness among participants of an elite sporting event during which 22 individuals became ill after eating a commercially catered buffet dinner in June 2012. All recalled eating fried rice which had been intended for lunch service earlier that day and 20 of the 22 reported eating chicken stir-fry. Though no food samples were available for analysis, laboratory analysis conducted on four faecal specimens resulted in *S. aureus* being cultured from one specimen and *S. aureus* enterotoxin detected in another. The known epidemiology of staphylococcal food poisoning suggests a food contaminated by an infected food handler which was subject to temperature abuse may have caused the outbreak. As *S. aureus* foodborne outbreaks are often underreported, this investigation is a valuable contribution to the evidence-base and understanding of foodborne illness due to *S. aureus* and staphylococcal enterotoxin.

Keywords: Staphylococcus aureus, enterotoxins, outbreak, foodborne, rice, chicken

## Introduction

Staphylococcal food poisoning (SFP) is a common cause of foodborne illness worldwide.[1-7] SFP occurs following ingestion of staphylococcal enterotoxins which are heat resistant and are produced in food following contamination by staphylococci, typically *Staphylococcus aureus*. Foods including sliced meat, meat products, salads, pastries, custards, raw milk and cheese products present a particular contamination risk.[2] Such a large population of staphylococci is indicative of unhygienic food handling procedures and temperature abuse over a period of time to allow for bacterial growth.[3]

In Australia, little published information exists describing past SFP outbreaks. OzFoodNet, however, collects information on all reported foodborne illness outbreaks. Between January 2000 and March 2012, OzFoodNet recorded 14 *S. aureus* outbreaks affecting 429 people (25 hospitalised; 1 death). In just under a third of these outbreaks, meals containing chicken were implicated. Twenty-nine per cent of these outbreaks were associated with food prepared by a commercial caterer (OzFoodNet Outbreak Register. June 2012. Unpublished data).

### The outbreak

On 2 June 2012, 22 individuals who had participated in an elite sporting event in Sydney experienced gastrointestinal symptoms after eating a buffet dinner served by the commercial catering company servicing the event. The day of the outbreak was the final day of the two week event and reportedly less busy at dinner time than previous meals. The 22 individuals were part of a larger cohort of up to 40 people who queued for dinner service earlier than the other 500 attendees due to the timing of their responsibilities at the event. Within hours of eating, all 22 fell ill with symptoms including vomiting, diarrhoea and abdominal cramping. Six people were transported to hospital. The event organiser reported that only the early dining group was affected.

This report summarises the epidemiological and microbiological investigations into the cause of the outbreak.

## Methods

### Epidemiological investigation

As this epidemiological investigation was conducted as part of the required public health response to a reported outbreak, it was not necessary to obtain ethical approval.

In order to develop hypotheses regarding the cause of the outbreak, preliminary interviews were conducted by telephone with several of the cases who attended the emergency department (ED) due to the severity of their symptoms. We drafted a food exposure questionnaire based on information from these interviews and information from a copy of the menu provided by the caterers. The questionnaire sought basic demographic details, food exposures (lunch and dinner), symptom description and duration, and illness history. Individuals were also

asked whether they were aware of anyone who had been ill with gastrointestinal symptoms prior to or following the outbreak.

A case was defined as anyone who ate the catered buffet dinner on 2 June 2012 at the early time (16:00 to 17:30) and experienced vomiting and/or diarrhoea and abdominal cramping commencing between 17:45 and 21:15. A confirmed case was someone meeting the case definition with *S. aureus* or *S. aureus* toxin detected in a stool specimen.

The names of the cases as well as others who were thought to have dined early were provided by the event organisers, Ambulance Service NSW, and other interviewed attendees. Based on the knowledge gleaned from these interviews, we conducted a retrospective cohort investigation to identify risk factors for developing illness. Interview data were collated and attack rates and risk ratios were calculated for specific food exposures. Analysis was conducted using SAS© software (version 9.3).

### Microbiological and environmental investigations

No food samples were available for testing. Faecal specimens were collected from 5 of the individuals who attended the ED. Initial testing for *Clostridium difficile, Salmonella, Shigella* and *Campylobacter* species and norovirus was conducted by the hospital laboratory.

Four specimens were available to be sent to Queensland Health Forensic and Scientific Services laboratory where they were cultured for a full range of enteric pathogens (including *Salmonella*, *Shigella* and *Campylobacter* species) and toxin-mediated foodborne illness causing bacteria (*S. aureus* and *Bacillus cereus*). Samples were cultured on Baird Parker Agar for two days at 37°C for *S. aureus* and Phenol-Red Egg Yolk Polymixin Agar for *B. cereus*. Three faecal samples were tested for staphylococcal enterotoxin using the Tecra enzyme-linked immunosorbent assay (TECRA). A site inspection was conducted by NSW Food Authority and is the subject of a separate internal report.

## Results

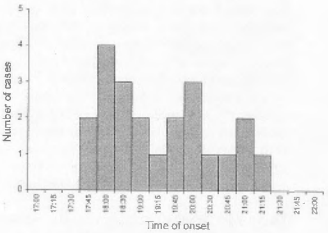
### Epidemiological results

A total of 36 persons who ate an early dinner served by the caterer were interviewed, with the majority interviewed 2 to 3 days after the incident. The median age of people interviewed was 40 years (range 12 to 72 years); 78% were female. Among the 36 persons interviewed, 22 (61%) were identified as cases, including two persons with laboratory-confirmed illnesses.

Of the 22 cases, 18 (82%) were female, ranging from 12 to 69 years old (median 34 years). Of those who did not fall ill, 10 (71%) were female, ranging from 21 to 72 years old (median 46 years).

Dinner times reported by cases ranged from 16:00 to 17:30. The epidemic curve illustrates the time distribution of symptom onsets among cases ranging over a 4 hour period on 2 June (Figure 1). Incubation periods ranged from 1 hour to 4.75 hours (average 2.5 hours). Illness typically began with the sudden onset of vomiting, followed by a period of concurrent vomiting and diarrhoea, with a median duration of 4 hours (range 2 to 13 hours). Of the 22 cases, 21 experienced vomiting (96%); 17 had diarrhoea (77%) and 10 reported abdominal cramping (46%). Six people (27%) were transported to a local ED. No interviewees were aware of others with symptom onset of gastrointestinal illness prior to or following the outbreak.

**Figure 1: Number of cases of gastrointestinal illness after the catered dinner on 2 June 2012, by time of onset (n=22)**




A number of food items were served during lunch and dinner. A selection of bread, cold meats (ham, chicken, turkey and silverside), salad and fried rice were available at lunch. Green salad, coleslaw, meatballs, cannelloni, boiled rice, fried rice, chicken stir-fry, bread rolls, jelly and yoghurt were served for dinner. Fried rice intended for lunch service on the day of the outbreak was reportedly served to the early diners because the boiled rice for dinner service was not ready in time.

All interviewees had eaten dinner early at the catered buffet while only 14 (39%) ate lunch there. Ninety-one per cent of cases ate both chicken stir-fry and fried rice at dinner with attack rates and rate differences of 74% for chicken stir-fry and 71% for fried rice (Table 1). The risk ratios for both dishes were undefined. Similarly, we were unable to conduct further analysis using stratification. Therefore it was not possible to identify an association with either chicken stir-fry or fried rice.

Table 1: Relative risks and attack rates for food items consumed by the cohort

| Exposure | Number who ate food | | | Number who didn't eat food | | | Risk ratio (95% CI) | p-value |
|---|---|---|---|---|---|---|---|---|
| | Ill | Total | Attack rate (%) | Ill | Total | Attack rate (%) | | |
| Salad | 5 | 7 | 71 | 17 | 29 | 59 | 1.22 (0.70-2.13) | 0.68 |
| Coleslaw | 2 | 2 | 100 | 20 | 34 | 59 | 1.70 (1.28-2.25) | 0.51 |
| Meatballs | 15 | 24 | 63 | 7 | 12 | 58 | 1.07 (0.61-1.89) | 1.00 |
| Cannelloni | 14 | 25 | 56 | 8 | 11 | 73 | 0.77 (0.47-1.27) | 0.47 |
| Fried rice | 22 | 31 | 71 | 0 | 5 | 0 | undefined | 0.005 |
| Chicken stir-fry | 20* | 27 | 74 | 0 | 7 | 0 | undefined | 0.0006 |
| Yoghurt | 5 | 8 | 63 | 17 | 28 | 61 | 1.03 (0.56-1.90) | 1.00 |
| Jelly | 8† | 13 | 62 | 13 | 22 | 59 | 1.04 (0.60-1.81) | 1.00 |
| Bread roll | 11‡ | 17 | 65 | 7 | 14 | 50 | 1.29 (0.69-2.43) | 0.48 |

* 2 missing
† 1 missing
‡ 5 missing

### Microbiological and environmental results

Initial screening results for all five specimens were negative for norovirus, *C. difficile*, *Salmonella*, *Shigella* and *Campylobacter* species.

Queensland Health Forensic and Scientific Services laboratory cultured *S. aureus* in one specimen. Another specimen tested positive for *S. aureus* enterotoxin.

Though no food samples remained for laboratory testing, the catering company confirmed that food handling policies were in place to prevent contamination as well as time and temperature abuse. No evidence of time and temperature abuse was observed during the site inspection. The catering company also reported that no staff members were known to be suffering from gastrointestinal illness during the sporting event.

## Discussion

*S. aureus* is one of the most common pathogens in humans, estimated to colonise approximately 25% of healthy adults.[2] Multiple pathogenic strains produce enterotoxins which, when ingested, can cause gastroenteritis.[8] In Australia, *S. aureus* intoxication accounted for 1% of all suspected and confirmed foodborne outbreaks reported to OzFoodNet between January 2000 and March 2012. Meals including chicken, beef, seafood, and lamb, as well as pasta salad and rice dishes have all been implicated as source of infection in these *S. aureus* enterotoxin outbreaks (OzFoodNet Outbreak Register. June 2012. Unpublished data).

Our findings suggested that chicken stir fry and/or fried rice were the food vehicles responsible for illness. Although it was not possible to determine risk ratios for fried rice and chicken stir-fry, the attack rates and rate differences calculated support this conclusion. It was not possible to consider these exposures independently as all cases who were able to recollect reported eating both food items.

SFP outbreaks result from contamination of food with *S. aureus* from food handlers either through skin infection on uncovered hands or arms, or via coughing or sneezing over food that is not subjected to further cooking. Current industry guidelines require food handlers to ensure their bodies, and anything from their bodies or clothing, do not contaminate food or food preparation areas.[9] For the bacteria to grow to sufficient numbers, the contaminated food must be left in temperature conditions where the bacteria are able to proliferate. *S. aureus* produces pre-formed toxins that have an emetic and diarrheal effect.[3]

In this investigation, there was no evidence of temperature abuse and we were unable to definitively identify a cause of the outbreak. The environmental investigation revealed no food safety breaches, and the absence of food samples made it impossible to identify the food vehicle responsible for the outbreak. The only apparent difference in foods served to the early diners was the fried rice which had been intended for lunch service.

To prevent toxin-based outbreaks, it is important that commercial food providers adhere to strict temperature protocols and ensure good food handling practices. Management and staff need to be alert to the presence of infected skin lesions or discharges from nasal passages, ears or eyes in food handlers. Appropriate measures should be taken to ensure that no ill individuals can contaminate food or food contact surfaces.[10]

Investigation of toxin-mediated foodborne illness is particularly problematic due to short onset times and duration of symptoms. Furthermore, as *S. aureus* is not a notifiable disease outbreaks often go undetected. This outbreak was only likely to have been reported due to the nature of the sporting event and the large number of individuals affected.

### Limitations

This investigation was limited in several ways. Though interviews were conducted as soon as possible following the outbreak, a number of individuals had difficulty remembering all foods consumed. A high proportion of individuals who dined early strongly believed that the fried rice intended for lunch was the infection source. Moreover, participants had extensively discussed the outbreak and theories on its cause, predominantly through social media, potentially introducing bias to the investigation.

The microbiological investigation was also impacted by limitations. Firstly, initial analyses of faecal specimens were restricted to in-house PCR assays and not cultured as per the NSW Health outbreak protocol which specifies that all faecal specimens related to potential outbreaks undergo routine enteric culture. Nevertheless, *S. aureus* is unlikely to be grown using routine culture, and the delay which ensued from the need to transport samples to Queensland for toxin testing would have decreased the yield when appropriately cultured there. Given the time delay between onset and receipt of the samples and the variable storage temperatures of the samples during that time, it is unsurprising that only 1 positive result was returned. This underlines the importance of good communication between public health investigators and laboratories so that specimens are tested according to the clinical and epidemiological picture. Additionally, vomitus specimens would have been preferable for analysis as staphylococcal enterotoxin is cleared from the gut quite quickly. Unfortunately, no samples of vomitus were collected as this is not a routine practice in EDs and vomiting had resolved before the public health investigation commenced.

## Conclusion

Information obtained from case interviews and the results of microbiological testing of human specimens support a conclusion that enterotoxigenic *S. aureus* bacteria were responsible for this outbreak. We were unable to definitively identify a food vehicle in this outbreak. *S. aureus* associated outbreak reports are rarely published in Australia despite being such a common cause of foodborne illness worldwide. This investigation improves our understanding of the epidemiology of foodborne *S. aureus* outbreaks in Australia.


## Acknowledgements

We are grateful to NSW Food Authority for conducting the environmental investigation; OzFoodNet for providing data on reported Australian gastrointestinal outbreaks due to *S. aureus* infection from the OzFoodNet Outbreak Register; Drs Martyn Kirk and Stephanie Davis of the ANU Master of Philosophy (Applied Epidemiology) program for guidance; NCIRS for providing us the time and resources to conduct the investigation; Jennie Musto for comments on the report; and the staff at Nepean Blue Mountains and Western Sydney Public Health Unit for support and assistance. We gratefully acknowledge the staff of Public Health Microbiology, Queensland Health Forensic & Scientific Services, who performed the technical work on these faecal samples.

NCIRS is supported by The Australian Government Department of Health, the NSW Ministry of Health and The Children's Hospital at Westmead.



## Author details

Ms Alexis Pillsbury, Master of Philosophy (Applied Epidemiology) Scholar[1,2]
Ms May Chiew, Master of Philosophy (Applied Epidemiology) Scholar [1,2]
Mr John Bates, Chief Scientist[3]
Dr Vicky Sheppeard, Medical Officer, Population Health [4,5]

1. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), The Children's Hospital at Westmead and the University of Sydney, New South Wales, Australia.
2. National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia.
3. Public Health Microbiology, Queensland Health Forensic and Scientific Services, Queensland Health, Archerfield, Queensland, Australia.
4. Nepean Blue Mountains and Western Sydney Public Health Unit
5. School of Public Health, University of Sydney

Corresponding author: Ms Alexis Pillsbury, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), Locked Bag 4001, Westmead, NSW 2145, Australia, Phone: (+61 2) 9845 1232, Facsimile: (+61 2) 9845 1418, Email: alexis.pillsbury@ health.nsw.gov.au


## References


1. CentersforDiseaseControlandPrevention(CDC),National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED). Staphylococcal food poisoning 2010 [updated June 7 2010]; Available from: http://www.cdc.gov/nczved/divisions/dfbmd/diseases /staphylococcal/
2. Heymann DL. Control of communicable diseases manual: American Public Health Association; 2008.

3. Hennekinne JA, De Buyser ML, Dragacci S. Staphylococcus aureus and its food poisoning toxins: characterization and outbreak investigation. *FEMS Microbiology Reviews*. 2012;36(4):815-36.
4. Osiyn A, De Buyser M, Guillier F, Groult J, Felix B, Salah S, et al. First evidence of a food poisoning outbreak due to staphylococcal enterotoxin type E, France, 2009. *Euro Surveill*. 2010;15(13):1-4.
5. Jelastopulu E, Venieri D, Komninou G, Kolokotronis T, Constantinidis T, Bontzos C. Outbreak of acute gastroenteritis in an air force base in Western Greece. *BMC public health*. 2006;6(1):254.
6. Asao T, Kumeda Y, Kawai T, Shibata T, Oda H, Haruki K, et al. An extensive outbreak of staphylococcal food poisoning due to low-fat milk in Japan: estimation of enterotoxin A in the incriminated milk and powdered skim milk. *Epidemiology and infection*. 2003;130(1):33-40.
7. Do Carmo LS, Cummings C, Linardi VR, Dias RS, De Souza JM, De Sena MJ, et al. A case study of a massive staphylococcal food poisoning incident. *Foodborne Pathogens & Disease*. 2004;1(4):241-6.
8. Lowy FD. Staphylococcal Infections. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012.
9. NSW Food Authority. Health and hygiene for food handlers. 2012 [updated 27 May 2011; cited 2012 October 31]; Available from: http://www.foodauthority.nsw.gov.au/industry/food-business-issues/health-and-hygiene-for-food-handlers/
10. Food Standards Australia New Zealand. Food Safety Standards - Health and hygiene: Responsibilities of food businesses: Chapter 3 (Australia only) Australia New Zealand Food Standards Code. 2012 [updated July 10 2012; cited 2012 July 23]; Available from: http://www.foodstandards.gov.au/scienceandeducation/factsheets/foodsafetyfactsheets/healthandhygieneresp102.cfm.

# REFERENCE

1. Heymann DL. Control of communicable diseases manual: American Public Health Association; 2008.

# APPENDIX

**Appendix 2.A. Food exposure questionnaire**


Health
Western Sydney
Local Health District

# Foodborne Illness

# Participant

**Elite Sporting Event**

**Saturday 3 June, 2012**

**SECTION 1: CONTACT DETAILS**

Surname: _____

First name: _____

Telephone: _____

**INTERVIEWER SCRIPT:**

*"Good morning/afternoon. My name is _____ and I'm calling from the Parramatta public health unit in Sydney. I was hoping to speak with _____(name of person/ guardian or parent)."*[1]

*"Hi _____ I'm ringing in regards to a number of people getting sick on Saturday 2 June at a Sydney sporting event. We are trying to investigate the source of the infection and were hoping that you would be able to answer questions regarding food consumed and health over the weekend. Your name was given to us by event organisers. It should take approximately ten minutes to complete this questionnaire. All the information we collect is confidential and only authorised public health staff will have access to this information. Would you be willing to answer our questions?"*

* If case unavailable, ask what is the best time to call back_____

Verbal consent given for interview:

Yes ☐

No ☐

[1] If participant was 15 years or under, consent was requested from parents/guardian. If consent was granted, the telephone interview was conducted in the presence of the parent/guardian.

**SECTION 2: PERSONAL DETAILS**

Age: ☐☐

Address: _____

Accommodation during championships: _____

Role at championships: _____

**SECTION 3: HEALTH INFORMATION**

*"Did you become ill with a gastrointestinal illness on the evening/night of 2June?"*

☐ Yes continue

☐ No skip remainder of the health information questions

*"What symptoms did you experience?"*

*"What time did your symptoms first start?"*

*"How long did your symptoms last?"*

*"Did you visit a hospital emergency department or general practitioner because of your illness?"*

☐
Yes

☐
No

*"If yes, which hospital?"*

*"Did the doctor at the hospital/ general practice take a specimen from you?"*

☐
Yes

☐
No

*"Were you aware of anyone who was ill with a similar illness prior to your getting sick?"*

☐
Yes

☐
No

*"Following your illness, were you aware of anyone close to you who subsequently became ill?"*

☐ Yes

☐ No

**SECTION 4: FOOD HISTORY**

*"Did you consume the following food during lunch service at the event?"*

| Food item | Response |
|---|---|
| Sandwiches | Yes ☐ No ☐ Unsure ☐ |
| Cold meat (ham, chicken, silverside, turkey) | Yes ☐ No ☐ Unsure ☐<br>"If yes, which meats?" _____ |
| Fried rice | Yes ☐ No ☐ Unsure ☐ |
| Bread rolls | Yes ☐ No ☐ Unsure ☐ |
| Wraps | Yes ☐ No ☐ Unsure ☐ |
| Gluten free bread | Yes ☐ No ☐ Unsure ☐ |

*"What time did you eat dinner?"*

*"Did you consume the following food during dinner service at the event?"*

| Food item | Response |
|---|---|
| Salad | Yes ☐ No ☐ Unsure ☐ |
| Coleslaw | Yes ☐ No ☐ Unsure ☐ |
| Meatballs | Yes ☐ No ☐ Unsure ☐ |
| Cannelloni | Yes ☐ No ☐ Unsure ☐ |
| Fried rice | Yes ☐ No ☐ Unsure ☐ |
| Boiled rice | Yes ☐ No ☐ Unsure ☐ |
| Chicken stir-fry | Yes ☐ No ☐ Unsure ☐ |
| Jelly | Yes ☐ No ☐ Unsure ☐ |

| | |
|---|---|
| Yoghurt | Yes ☐ No ☐ Unsure ☐ |
| Bread roll | Yes ☐ No ☐ Unsure ☐ |

*"Were other food items consumed during and between lunch and dinner?"*

☐
Yes

☐
No

*"If yes, what food items?"*

*"That concludes the interview. Thank you for your time and co-operation .Do you have any questions or comments regarding the interview?"*

*"If you have any questions please do not hesitate to call any one from the infectious disease team at Parramatta public health unit on 9840 3603.*

# CHAPTER 3. OUTBREAK INVESTIGATION & RESPONSE

## Tracing lines of transmission in a measles outbreak, Western Sydney, New South Wales, 2012

# TABLE OF CONTENTS

# PREFACE

## Background and scope of the chapter

In 2012, New South Wales (NSW) experienced its largest measles outbreak since 1998 and the country's largest since 1997. The outbreak initiated in Western Sydney in April 2012. Following the initial measles notification, I was requested by the Western Sydney Public Health Unit (PHU) to assist with the public health response.

In early May, a cluster of infections occurred at the Emergency Department (ED) of the Children's Hospital at Westmead (CHW). The PHU invited me and my Master of Philosophy Applied Epidemiology (MAE) and National Centre for Immunisation Research and Surveillance (NCIRS) colleague Ms May Chiew to investigate the source of infection.

This chapter describes the NSW 2012 measles outbreak and the ensuing public health response effort, including the investigation into the CHW infection source.

## Investigatory role

Contributing to the Western Sydney outbreak response effort, I assisted with contact tracing, conducting rapid risk assessment of exposed individuals to provide them with appropriate advice regarding risk potential, signs of infection, and post-exposure preventative measures when appropriate. I also aided with the planning and execution of several post-exposure prophylaxis (PEP) clinics convened to distribute measles-mumps-rubella (MMR) vaccine or normal human immunoglobulin (NHIG) injections to those for whom such preventative measures were deemed appropriate.

Investigating the infected cluster's source involved several key elements. Firstly, liaising with ED personnel to understand the ED layout (Appendix 3.B), likely patient movements, and case notes. Secondly, reviewing patient records and designing and implementing an algorithm to methodically narrow down a list of potential source

cases. Finally, drafting a questionnaire and interviewing the parents/guardians of potential sources of infection (Appendix 3.A). These elements of the investigation were conducted equally by myself and Ms Chiew. Additionally, we co-wrote elements of the 'Methods' and 'Results' sections of the report which follows. Also with Ms Chiew, and with Dr Shopna Bag, I co-wrote and delivered a presentation to the NCIRS Journal Club and the CHW Infectious Disease Meeting detailing the outbreak and response effort, as well as aspects of measles epidemiology responsible for the propagation of the recent outbreak (Appendix 3.C).

## Lessons learned

First and foremost, participating in the outbreak response effort at the local level required a crash course in measles virology, clinical features and epidemiology. This included attending to a measles case presenting to one of our PEP clinics with full-blown maculopapular rash. It was a rare opportunity. In this post-elimination era where cases are few, even clinicians seldom witness such cases firsthand, let alone epidemiology trainees.

Participating in the response effort was fantastic exposure to hands-on public health work. I have now experienced first-hand the time and energy required for outbreak response at this level, and learned that contact tracing and follow-up can be a massive, exhausting and sometimes seemingly thankless job. Moreover, the response effort made apparent the importance of skilfully communicating health information to the public in an instructive, confident and calm manner.

Conducting the investigation into the source of infections at the CHW ED further enhanced my ability to design and implement a field investigation. Having toured several hospital EDs as part of this investigation, I better appreciate the reasons EDs persist as common transmission locations during outbreaks, and the challenges inherent in rectifying this. These will be elaborated upon in more detail both in this chapter and the next.

Finally, investigating this piece of the wider NSW 2012 measles outbreak reinforced

the challenges in conclusively 'tying up' every known measles exposure during an outbreak and therefore how difficult achieving and maintaining elimination status may be. Furthermore, it stressed to me the distinct value of genotyping to proving epidemiological links and thereby assisting in achieving measles elimination.

## Public health impact

Local public health responses are an important source of community protection against infectious diseases like measles. Skilled, effective and timely responses to outbreaks at the local level are also vital for achieving ratification of measles elimination status as defined by the World Health Organization (WHO).[1] Elimination status requires not only the cessation of endemic measles transmission but also ensuring sustained transmission following the importation of a measles case is limited. Consequently, ascertaining the origins of infection of each notified measles case, along with tracing all possible lines of transmission, is imperative. In this way, our investigation into the CHW ED source of infection constituted an important contribution to the Australian public health response effort in this era of measles elimination.

## Acknowledgements

I am extremely grateful to Dr Vicky Sheppeard who invited and entrusted me to participate in the Western Sydney PHU response. During my participation, she was a fantastic mentor and watching her lead the Western Sydney response was a valuable learning experience. Dr Shopna Bag and other members of the PHU team were extremely instructive and patient with my inexperience. Several individuals at the CHW assisted the investigation conducted by Ms Chiew and me. Specifically, CHW ED Director Mary McCaskill and the Acting Nurse Unit Manager of the ED Samantha Mihailovich were patient in answering our many questions and providing us with useful information, including guided tours throughout the ED. Also, Robert Robinson, the Clinical Nurse Consultant for Infection Control at Blacktown Hospital, and Marty

Bodsworth, the Emergency Department FirstNet Data Manager for the Blacktown Hospital ED, assisted our investigation of potential links between cases.

I am grateful that my supervisors at NCIRS supported my participation in the PHU's work and were eager to learn about the outbreak from my experiences with, and connections to, the response effort. Lastly, Associate Professor Kristine MacCartney of NCIRS provided helpful clinical guidance regarding the direction of our investigation.

# ABBREVIATIONS

| | |
|---|---|
| **ACIR** | Australian Childhood Immunisation Register |
| **CHW** | The Children's Hospital at Westmead |
| **ED** | Emergency Department |
| **GP** | General Practice |
| **IgG** | Immunoglobulin G |
| **IgM** | Immunoglobulin M |
| **LHD** | Local Health District |
| **MAE** | Master of Philosophy Applied Epidemiology |
| **MMR** | Measles-Mumps-Rubella (Vaccine) |
| **MRN** | Medical Record Number |
| **NCIRS** | National Centre for Immunisation Research & Surveillance |
| **NHIG** | Normal Human Immunoglobulin |
| **NMSS** | National Measles Surveillance Strategy |
| **NSW** | New South Wales |
| **PEP** | Post-Exposure Prophylaxis |
| **PHU** | Public Health Unit |
| **SoNG** | Series of National Guidelines |
| **WHO** | World Health Organization |

# LIST OF TABLES

# LIST OF FIGURES

# ABSTRACT

## Introduction

In April 2012, an imported measles case notified to the Western Sydney Local Health District (LHD) began what would become the nation's largest outbreak since 1997. This report describes the beginning of this outbreak and the local level response effort and details the specific investigation into the source of transmission that resulted in a small cluster of cases infected in a paediatric ED.

## Methods

All notified measles cases, including the cluster exposed in the paediatric ED, were followed up according to national guidelines. To investigate the infective source of the cluster, an investigatory algorithm was designed and implemented which methodically narrowed down potential sources of infection. This included a review of ED layout and the movements and timelines of secondary cases within the ED. The records of potential source cases were reviewed to exclude those with incompatible symptoms or timelines. The parents/guardians of potential source cases were interviewed using a questionnaire designed for this investigation.

## Results

For the cluster of cases, 270 contacts required follow-up. Of the 162 children who presented to the ED on 11 May 2012, we excluded 92 as potential sources of infection based on the timing of their presentations. Additionally, we excluded 17 children who presented with conditions incompatible with measles. Following other preliminary exclusions, medical charts were reviewed for the remaining 40 patients, excluding 26 for symptoms/diagnoses incompatible with measles and nine who were fully immunised. Five potential cases were proxy interviewed; however, none was assessed as having had measles or measles-like illness at the time of presentation to the ED.

## Conclusion

Despite failing to identify the source of infection for the cluster infected in the

paediatric ED on the same day, this report describes important components of the outbreak and response effort, emphasises the potential for transmission to occur in EDs, and highlights characteristics of EDs and ED work which may facilitate transmission. Moreover, investigations such as this which attempt to trace chains of transmission are critical for measles elimination efforts.

# TRACING LINES OF TRANSMISSION IN A MEASLES OUTBREAK, WESTERN SYDNEY, NEW SOUTH WALES, 2012

**Ms Alexis Pillsbury**[1,2], Master of Philosophy (Applied Epidemiology) Scholar

Ms May Chew[1,2], Master of Philosophy (Applied Epidemiology) Scholar

Affiliation(s)

1. National Centre for Immunisation Research and Surveillance (NCIRS), The Children's Hospital at Westmead and the University of Sydney, New South Wales, Australia.
2. National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australia.

# INTRODUCTION

Measles is an extremely infectious illness caused by the Paramyxovirus, genus Morbillivirus. Transmission is airborne, spread by respiratory secretions.[2] Measles infection and resulting complications can be severe. Because of its severity, measles is a notifiable disease in Australia and a confirmed case requires laboratory definitive evidence of measles infection, or clinical and epidemiological evidence.[3]

Measles vaccination has been recommended in Australia since the mid-1970s, with a formal control campaign established in 1998 to prepare the country for measles elimination. The National Measles Surveillance Strategy (NMSS) has successfully reduced the incidence of measles in Australia by striving to maintain 95% vaccination coverage throughout each new birth cohort.[4] Improvements to surveillance and vaccination policy—including targeted school-based catch-up campaigns—have greatly assisted the country with its goal of WHO-certified elimination. While evidence suggests that the disease has been eliminated from Australia since the end of the 1990s,[5] this status has not been formally ratified.

Despite decreased incidence, outbreaks initiated by imported cases continue to persist,[4] highlighting weaknesses in vaccination coverage, vulnerable demographics and infection control failures (Figure 3.1 and Figure 3.2).

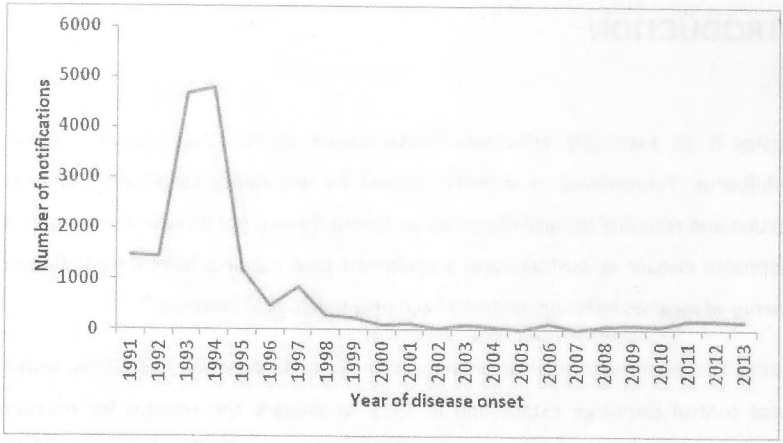



**Figure 3.1. Number of measles notifications, Australia, 1991–2012**[6]

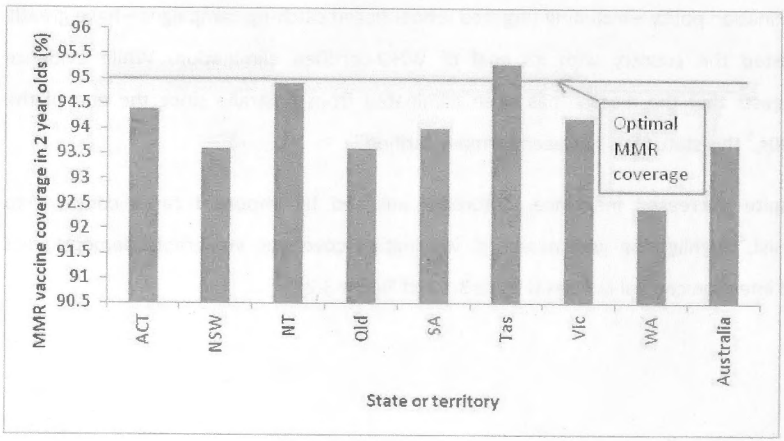



**Figure 3.2. MMR vaccination coverage (%) in 2 year olds (birth cohort 1 January–31 March 2011), Australia, by state and territory, 2013**[7]

Transmissions in recent outbreaks have commonly occurred in healthcare settings, particularly hospital EDs.[8, 9] EDs tend to be crowded, busy environments where those susceptible (eg, the immunocompromised and under-vaccinated) can potentially be exposed to individuals presenting with the virus.[8] In developed countries like Australia,

the relatively low incidence of measles means clinicians often misdiagnose what is for many of them an unfamiliar disease. This often results in delayed implementation of control strategies, providing time for outbreaks to persist.

On 16 April 2012, the Western Sydney LHD was notified of a confirmed measles case. The case was a 25 year old Australian born male who had contracted measles on holiday in Thailand. He had returned to Australia on 30 March; symptoms began on 7 April with a sore throat and cough. He attended a General Practice (GP) clinic on 9 and 12 April but was not diagnosed with measles. On 13 April, a rash appeared and he presented to a local ED where he was triaged and admitted. He was not isolated and remained in the ED from 8:00 until 17:00. At the time of ED attendance, he had a fever of 39.5°C, conjunctivitis, cough, coryza and a maculopapular rash. The patient was eventually confirmed IgM (immunoglobulin M) positive and IgG negative.

Following diagnosis, the patient was questioned by public health staff regarding his immunisation status and potential contacts. The patient professed to be fully immunised. It is possible, however, that due to his age (born in 1986), he missed out on the school-based catch-up immunisation campaign. He infected several others (referred to as 'cluster 1' in this report) before being diagnosed.

This was the beginning of what was to become the largest outbreak in New South Wales (NSW) since 1998 and Australia's largest outbreak since 1997, with 168 cases notified between April and November 2012 (Figure 3.3)[6,10] Ninety-two percent (n=156) of cases occurred in Western and South Western Sydney. Twenty-nine percent (n=49) of cases were among those aged 10–19 years. Seventy-six percent (n=128) of cases reported unsure or no vaccination status, though 21.4% (n=36) were infants aged <1 year who were too young to be vaccinated. Pacific Islanders represented a large proportion of cases at 21.4% (n=36). Cases acquired in a healthcare setting comprised 21.4% of cases (n=36).[11]

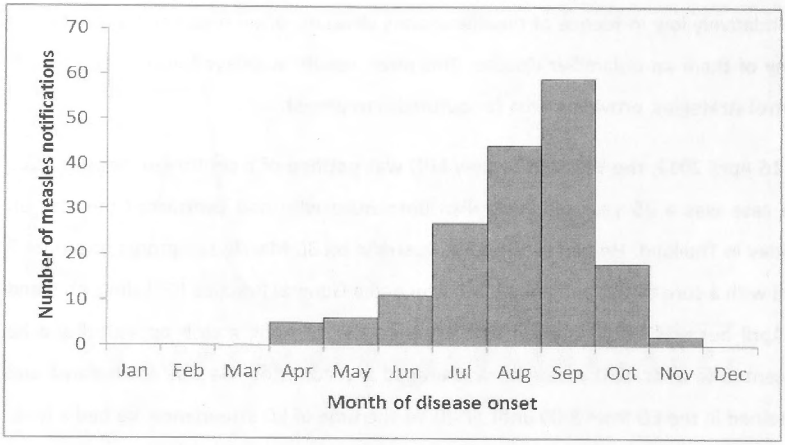



**Figure 3.3. Number of measles notifications, NSW, 2012**[10]

This report describes the investigation conducted to identify the source of infection for a cluster of four cases (referred to as 'cluster 2' in this report) infected in the CHW ED on 11 May in the context of the beginning stages of the state-wide outbreak and the local level response effort. This cluster was likely linked indirectly to the index case and 'cluster 1'.

# METHODS

## Case identification, follow-up and management

The *NSW Public Health Act 2010* requires doctors and laboratory clinicians to notify all measles cases to the local PHU.[12] In accordance with the national guidelines, both confirmed and probable cases are to be notified.[13] Confirmed cases require either laboratory definitive evidence or a combination of both clinical and epidemiological evidence.[14] For the purposes of the state-wide outbreak, all cases with a symptom

onset between 7 April and 29 November with an established epidemiological link to Western Sydney or Sydney South Western LHDs with no history of recent overseas travel and a D8 or unknown genotype were defined as outbreak cases.

Case investigation and public health response followed national guidelines. Vaccination status was confirmed when possible through the Australian Childhood Immunisation Register (ACIR) for those aged 16 and under. Once a case was notified, contacts were followed up and preventative measures in the form of vaccination or NHIG were recommended and offered when appropriate. Other control and prevention mechanisms including alerts distributed to health facilities, media briefs and emergency vaccination clinics held in high-risk areas were enacted throughout the course of the outbreak.

Following the notification of the index case, public health staff interviewed the index case to determine the case's movements and identify any exposed contacts. Individuals who could be identified to have been in the same location as the index case at the same time or up to two hours after the index case departed were followed up. Any other subsequent infections were identified via notification to the PHU. Those who were identified who had an onset of illness 7–18 days after contact with the index case were presumed to be epidemiologically linked to the index case.

## Investigation into the source of infection of the CHW ED cluster

Four measles notifications were received within a six day period and it was revealed via interviews that all four had been present in the CHW ED on 11 May. These 'primary cases' were defined as those four cases which were notified to the PHU and who had been present in the CHW ED on 11 May with an onset of illness compatible with having been exposed on 11 May. It was presumed that these cases acquired their infection from a common source and an investigation into the probable source case was launched. 'Probable source case' was defined as a case who, while infectious, had contact with a notified primary case, with the contact between the two occurring

within a timeframe compatible with the incubation period of the primary case. Similar to the index case and the first cluster of cases, control procedures for this second cluster of cases followed Australian national guidelines.

The ED Director supplied an electronic list of all ED attendances for 11 May 2012 which included Medical Record Number (MRN), date of birth, times of arrival, triage and departure. Electronic ED patient notes were accessed to review details regarding presenting condition, history, provisional diagnosis and discharge. The ACIR was consulted for individuals' immunisation status when appropriate.

The complete list of attendees for 11 May was pared down according to the times that individuals were present in the ED. Current national protocols stipulate that contacts be followed up for up to two hours after the index case has departed.[13] Based on these guidelines, patients were excluded as probable source cases if they were discharged before 19:00 as they would not have been able to infect Case 3 if they departed any earlier. Patients were also excluded if they arrived in the ED waiting room after 21:30 as they would not have been able to infect Case 4 who was discharged to a ward at 21:20.

The complete list of attendees was further restricted by presenting condition (Figure 3.7). Patients whose presenting problems included trauma, mental health issues, central nervous system symptoms, urological symptoms, constipation, appendicitis, routine childhood examination and dental concerns were excluded.

Having excluded those who did not fit the timeframe detailed above or those whose conditions were not compatible with measles, the remaining patients were closely assessed according to symptoms recorded in hospital notes and immunisation status obtained from the ACIR. A suspect case was defined as any patient that presented with fever and other symptoms consistent with measles (cough; coryza; conjunctivitis; rash) who was unvaccinated or partially vaccinated for measles. Children listed as 'did not wait' were reviewed by immunisation status and symptoms. If no information was present, their parents were contacted for an interview (Appendix 3.A).

Additionally, in an attempt to determine whether a more precise location of exposure

within the ED could be determined, we attempted to recreate the movements of cases within the ED using ED notes, an ED map (Appendix 3.B) and the hospital's official incident report. Though three of the confirmed cases had waited in the ED waiting room before being examined by ED staff, Case 4 was brought in by ambulance using an alternate entrance. This information assisted us to further hone in on the probable time and location of exposure as well as to rule out anyone who had not actually entered the ED.

# RESULTS

## Case identification and follow-up

During follow-up of the outbreak's index case, the PHU received notification of three other cases who were epidemiologically linked to the index case, including the index case's 11 month old nephew and a 22 year old male with whom he had played team sports. A separate notification was received by the PHU of a 34 year old male who had been in the ED of a large area hospital at the same time as the index case (Figure 3.4). This case was overlooked in contact tracing efforts as his name had not appeared on lists provided to the PHU by the hospital. Following this initial cluster of cases ('cluster 1') directly linked to the index case, a subsequent cluster of four notifications ('cluster 2') was received by the PHU within six days (Figure 3.5).

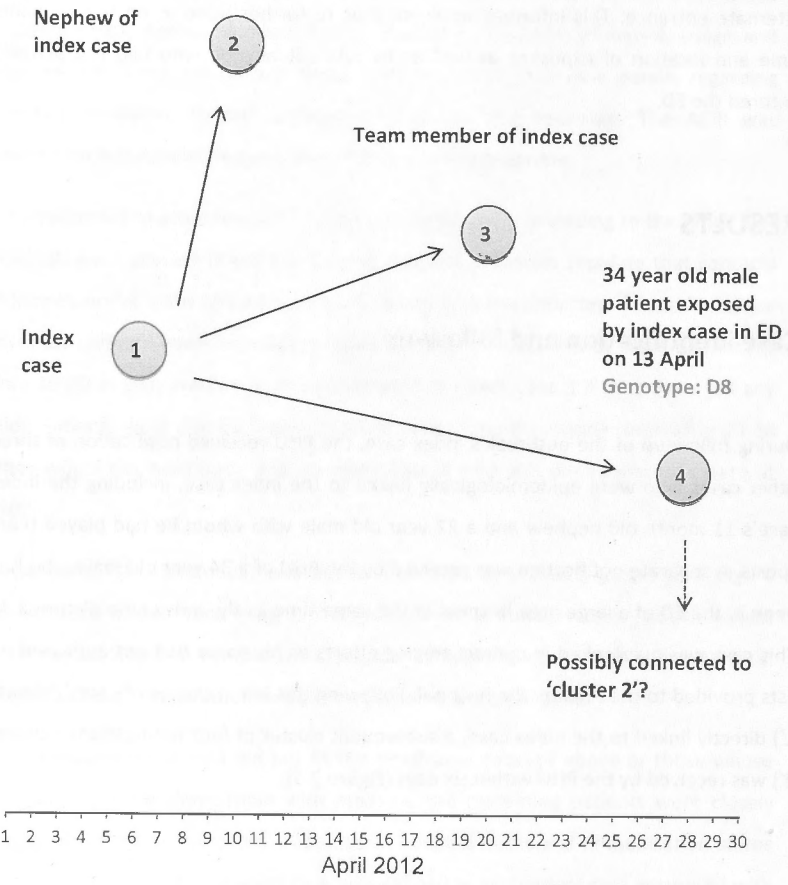



**Figure 3.4. Timeline of 'cluster 1' measles onset dates and lines of transmission, Western Sydney LHD, April 2012**

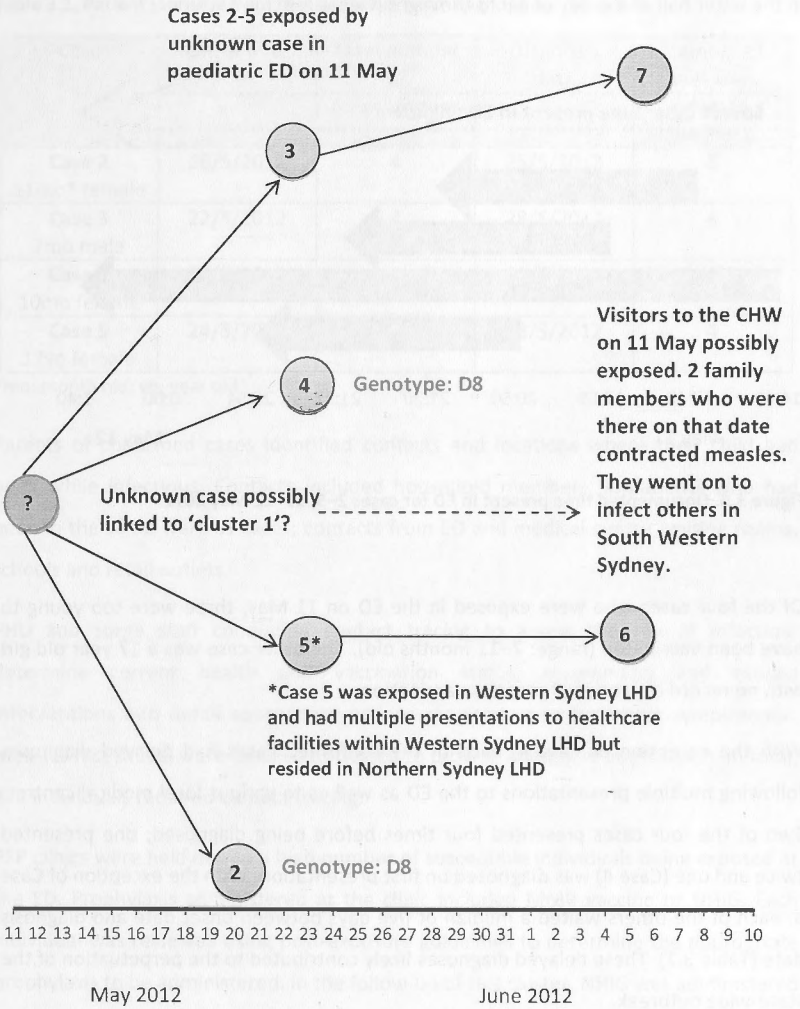



**Figure 3.5.Timeline of 'cluster 2' measles onset dates and lines of transmission, Western Sydney LHD, May/June 2012**

Interviews with parents/guardians of these four primary notified cases revealed that all had been present in the CHW ED on 11 May. All four cases had illness onset which was compatible with having been exposed on 11 May. All four were present in the ED

in the latter half of the day and into the night (Figure 3.6).

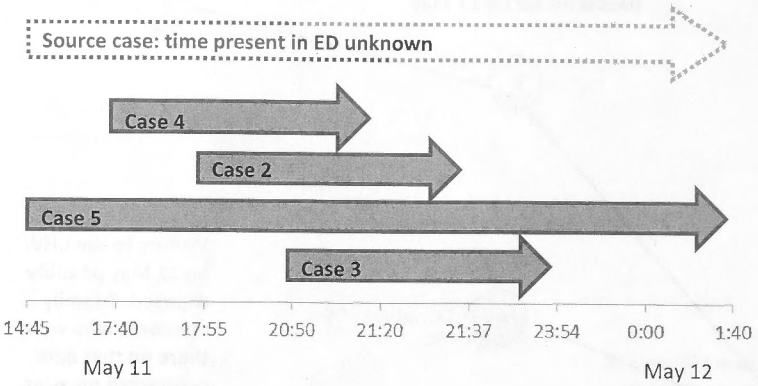



**Figure 3.6. Documented time present in ED for cases 2–5, 11–12 May 2012**

Of the four cases who were exposed in the ED on 11 May, three were too young to have been vaccinated (range: 7–11 months old). The other case was a 17 year old girl with no record of receipt of measles vaccinations.

With the exception of Case 4, each of the confirmed cases had delayed diagnoses following multiple presentations to the ED as well as to various local medical centres. Two of the four cases presented four times before being diagnosed; one presented twice and one (Case 4) was diagnosed on first presentation. With the exception of Case 4, each of the others waited a median of five days between onset date and diagnosis date (Table 3.1). These delayed diagnoses likely contributed to the perpetuation of the state-wide outbreak.

**Table 3.1. Patient journeys from measles onset until diagnosis for cases 2–5**

| Case | Onset date | Total number of presentations | Diagnosis date | Number of days from onset to diagnosis |
|---|---|---|---|---|
| **Case 2** 11mo* female | 20/5/2012 | 4 | 25/5/2012 | 5 |
| **Case 3** 7mo male | 22/5/2012 | 4 | 28/5/2012 | 6 |
| **Case 4** 10mo female | 23/5/2012 | 1 | 24/5/2012 | 1 |
| **Case 5** 17yo female | 24/5/2012 | 2 | 28/5/2012 | 4 |

*mo: month old; yo: year old

Parents of confirmed cases identified contacts and locations where their child had been while infectious. Contacts included household members; in-patients who had been in the same ward as cases; contacts from ED and medical centre waiting rooms, schools and retail outlets.

PHU and surge staff conducted contact tracing to assess the risk of infection; determine current health and vaccination status; recommend and explain interventions and detail appropriate actions required upon becoming symptomatic. Measles fact sheets were emailed or posted to provide additional information. In total, 270 individuals required contact tracing.

PEP clinics were held due to a high number of susceptible individuals being exposed at the ED. Prophylaxis administered at the clinic included MMR vaccine or NHIG. Each individual was reviewed using post-exposure guidelines to determine the appropriate prophylaxis to be administered. In the follow-up of this cluster, NHIG was administered to 18 exposed individuals; 8 were recommended to receive MMR vaccine. One hundred letters were sent to those who could not be reached in person during contact tracing efforts. Additional alerts were administered by the school of the 17 year old case to all students and to area schools whose students had attended a recent school formal the case had attended while infectious.

## Investigation into the source of infection for the CHW ED cluster

There were 162 children who presented to the ED on 11 May 2012 of which 92 were excluded as probable source cases based on the timing of their presentations (Figure 3.7). The four confirmed measles cases were also excluded, resulting in 66 remaining children. Additionally, 17 children who presented with conditions which were incompatible with measles were excluded. Other preliminary exclusions included nine patients who did not wait: three fully immunised patients, three afebrile patients, and three who were followed up by ED staff.

The ED medical charts for the remaining 40 patients were reviewed. Of these, a number of patients were excluded as they were afebrile (n=23); had received two doses of MMR (n=9); were diagnosed with cervical lymphadenopathy and tonsillitis (n=1), Respiratory Syncytial Virus (n=1) and meningococcal infection (n=1).

Phone interviews with parents of five suspect patients were conducted. The median age of suspect cases was 17 months (range: 9 months–7 years). All five suspect patients were reported to have recovered soon after presentation at the ED. One patient had recently been exposed to a sporadic case of measles at a local medical centre; however, the sporadic case was later identified as genotype B3.

Interviews did not yield a source case. The parents/guardians of all five suspected patients reported that their child had received other diagnoses and had improved upon prescribed treatment; had not had other measles-like symptoms beyond those identified in their charts; or was immunised.

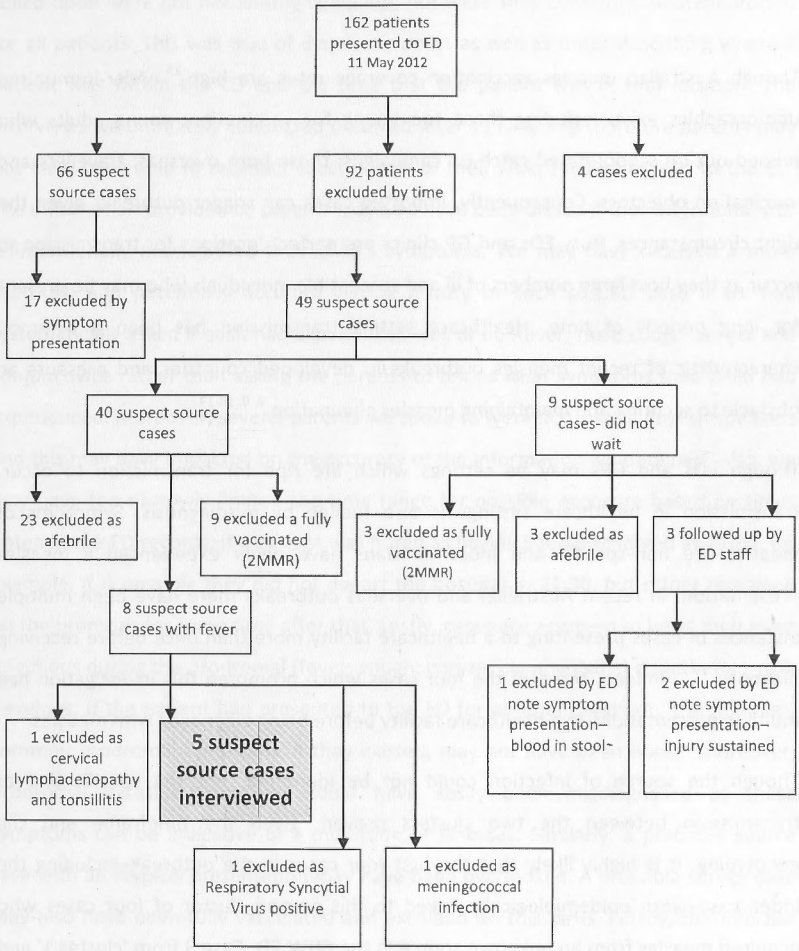



**Figure 3.7. Algorithm used to identify suspect measles source cases responsible for the CHW ED exposure on 11 May 2012**

# DISCUSSION

Though Australian measles vaccination coverage rates are high,[15] under-immunised demographics exist, including those too young for vaccination; young adults who missed out on school-based catch-up campaigns; those born overseas; travellers and vaccination objectors. Consequently, imported cases can trigger outbreaks given the right circumstances. Busy EDs and GP clinics are perfect locations for transmission to occur as they host large numbers of ill and susceptible individuals who may be present for long periods of time. Healthcare setting transmission has been a common characteristic of recent measles outbreaks in developed countries and presents an obstacle to securing and maintaining measles elimination.[8, 9, 16-19]

Though EDs and GPs may be settings which are ripe for transmission to occur, transmission in healthcare settings is also fuelled by misdiagnosis. Symptoms of measles are non-specific and most clinicians have never experienced a measles presentation. In recent Australian and overseas outbreaks there have been multiple instances of cases presenting to a healthcare facility more than once before receiving diagnosis.[19-21] Indeed, three of the four cases which prompted this investigation had multiple presentations to a healthcare facility before being diagnosed with measles.

Though the source of infection could not be identified, nor the specific line of transmission between the two clusters proven, given the timeframe and the genotyping, it is highly likely that the first four cases in the outbreak–including the index case–were epidemiologically linked to this second cluster of four cases who acquired measles from an unknown source in the CHW ED. Case 3 from 'cluster 1' and cases 2 and 4 from 'cluster 2' were all D8 genotype; D8 is commonly found in Southeast Asia.[22] The common genotype makes it more likely, too, that the second cluster was infected by a common source on 11 May when the cluster overlapped in location and time. This highlights the importance of genotyping not only for establishing lines of transmission during an outbreak but also for determining that an outbreak was imported, which is crucial for verifying elimination of the disease.

This investigation was limited in several ways. First, the ED medical records that we relied upon were not necessarily complete, nor were they consistent or standardised for all patients. This was true of diagnostic notes as well as notes describing where a patient was within the ED and the time that the patient was in that location. The interviews we ultimately conducted occurred after 11 May and therefore parents may not have been able to recollect exact details of their child's illness or visit to the ED. The information provided by parents may also have been biased if they intentionally or unintentionally misclassified their child's symptoms. We may have received a more thorough and potentially accurate clinical history of each suspect case if we had systematically asked if each had experienced–yes or no–fever, rash, cough, coryza and conjunctivitis rather than asking the parents to tell us what symptoms their child had experienced. Moreover, several parents we spoke to were non-native English speakers and this may have impacted on the accuracy of the information we obtained. Also, we may have too narrowly limited the time range for possible exposure based on times noted in the ED records. If a patient was noted as having been discharged at 21:30, for example, it is possible they did not depart the hospital at 21:30, but rather remained on the premises for some time after that. Lastly, cases are assumed to be at their most infectious during the prodromal (fever; cough; coryza; conjunctivitis) stage before rash develops. If the patient had presented to the ED for another condition, the relatively common prodromal symptoms, if they existed, may not have been noted. Moreover, prodromal measles symptoms could have easily been misdiagnosed as these symptoms can be indicative of a multitude of illnesses. Similarly, a probable source case with an atypical presentation may have been overlooked. A probable source case may also have been fully vaccinated and excluded on this basis. Finally, the infected 'source' individual may not have been a patient included on our original list.

Missing the opportunity to quickly diagnose and isolate a single case of measles can perpetuate large-scale and costly outbreaks like the 2012 NSW outbreak—the country's largest since 1997.[6] Investigating all measles infections and lines of transmission where possible assists Australia's goal of maintaining and ultimately ratifying elimination status. Moreover, detailing cases of healthcare transmissions such as those described in this report may raise awareness about how and why healthcare

settings continue to be common locations for transmissions during outbreaks. This in turn may highlight specific lessons to be learned regarding improving infection control and response in future outbreaks.

## RECOMMENDATIONS

The following are broad recommendations for improving future control and response efforts based on participation in the local public health response effort. Additional recommendations specific to control and prevention of transmissions in healthcare settings appear in Part Two of Chapter 4.

1. Given the time and resource intensiveness of the contact tracing effort, a thorough cost-effectiveness analysis following the conclusion of the outbreak would be beneficial in order to inform policy decisions surrounding future outbreak response efforts.

2. An evaluation of the effectiveness of any campaigns which were held to educate members of the public–particularly specific ethnic groups–about the existence of the measles outbreak and the importance of immunisation would also be beneficial. For example, this could include evaluation of the effect of media campaigns and immunisation clinics targeting Pacific Islander communities. Evaluation should include a cost-effectiveness component.

3. Periodic refresher training of health practitioners likely to be involved in future outbreak control efforts may ensure that future efforts can proceed more efficiently and may also assist by spreading awareness of measles symptoms and epidemiology during non-outbreak times. Training could include measles immunology and control guidelines.

4. Social research examining under-immunised demographic groups to better understand the barriers to improving vaccination uptake in these groups could inform strategies for targeted vaccination campaigns as well as strategies for targeting

awareness/education campaigns during future outbreaks.

# REFERENCES


1. World Health Organization (WHO). Global measles and rubella strategic plan: 2012-2020. Switzerland2012.

2. Heymann DL. Control of communicable diseases manual: American Public Health Association; 2008.

3. Department of Health and Ageing. Australian national notifiable diseases case definitions: Measles case defintion. [updated 12 March, 2004; cited 2012 17 August]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_measl.htm.

4. Martin N, Foxwell AR. Measles status in Australia, and outbreaks in the first quarter of 2009. Commun Dis Intell. 2009;33(2):225-31.

5. Heywood A, Gidding HF, Riddell MA, McIntyre PB, MacIntyre CR, Kelly H. Elimination of endemic measles transmission in Australia. Bull World Health Organ. 2009;87:64-71.

6. National Notifiable Diseases Surveillance System (NNDSS). Number of notifications of measles, received from state and territory health authorities in the period of 1991 to 2012 and year-to-date notifications for 2013. Canberra 2013.

7. National Centre for Immunisation Research and Surveillance (NCIRS). Childhood immunisation coverage estimates. [Internet] 2013 [cited 2014 January 2]; Available from: http://ncirs.edu.au/immunisation/coverage/estimates/.

8. Botelho-Nevers E, Gautret P, Biellik R, Brouqui P. Nosocomial transmission of measles: An updated review. Vaccine. 2012;30(27):3996-4001.

9. Bowen AC, Ferson MJ, Palasanthiran P. Consequences of an unrecognized measles exposure in an emergency department. Emergency Medicine Australasia. 2009;21(6):491-6.

10. NSW Health. Measles notifications in NSW residents. [Internet] 2013 [cited 2013 February 15]; Available from: http://www0.health.nsw.gov.au/data/diseases/measles.asp.

11. Najjar Z, Hope K, Clark P, Nguyen O, Rosewell A, Conaty S. Sustained outbreak of

measles in New South Wales, 2012: risks for measles elimination in Australia. Western Pac Surveill Response J. 2013;5(1):1-7.

12. NSW Government. Public Health Act 2010 (NSW). [Internet] 2013 [cited 2013 December 4]; Available from: http://www.legislation.nsw.gov.au/maintop/view/inforce/act+127+2010+cd+0+N.

13. Australian Government Department of Health and Ageing. Series of national guidelines. Measles. National guidelines for public health units. . 2009 [updated 19 February 2009; cited 2012 21 November]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/55AD336B864C7203CA25755F000307B6/$File/measles-song.pdf.

14. Australian Government Department of Health and Ageing. Australian national notifiable diseases case definitions: measles case definition. [Internet] 2004 [cited 2013 February 22]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_measl.htm.

15. Hull B, Dey A, Mahajan D, Menzies R, McIntyre PB. Immunisation coverage annual report, 2009. Commun Dis Intell. 2011;35(2):132-48.

16. Chen SY, Anderson S, Kutty PK, Lugo F, McDonald M, Rota PA, et al. Health Care-Associated Measles Outbreak in the United States After an Importation: Challenges and Economic Impact. Journal of Infectious Diseases. 2011;203(11):1517-25.

17. Choi WS, Sniadack DH, Jee Y, Go UY, So JS, Cho H, et al. Outbreak of measles in the Republic of Korea, 2007: Importance of nosocomial transmission. Journal of Infectious Diseases. 2011;204(suppl 1):S483-S90.

18. Groth C, Bottiger B, Plesner A, Christiansen A, Glismann S, Hogh B. Nosocomial measles cluster in Denmark following an imported case, December 2008-January 2009. Euro surveillance. 2009;14(8).

19. Weston KM, Dwyer DE, Ratnamohan M, McPhie K, Chan S, Branley JM, et al. Nosocomial and community transmission of measles virus genotype D8 imported by a returning traveller from Nepal. Communicable Diseases Intelligence. 2006;30(3):358.

20. Davidson N, Andrews R, Riddell M, Leydon J, Lynch P. A measles outbreak among young adults in Victoria, February 2001. Communicable Diseases Intelligence.

2002;26(2):273-8.

21. Kantele A, Valtonen K, Davidkin I, Martelius T, Vozelevskaja N, Skogberg K, et al. Travellers returning with measles from Thailand to Finland, April 2012: infection control measures. Eurosurveillance. 2012;17(22).

## APPENDICES

Appendix 3.A. Questionnaire for CHW cluster investigation


Health
Western Sydney
Local Health District

# Measles Suspected Source of Infection Questionnaire

Paediatric Hospital Emergency Department Western Sydney

11 May 2012

**SECTION 1: CONTACT DETAILS**

Surname: _____

First name: _____

Telephone: _____

**INTERVIEWER SCRIPT:**

*"Good morning/afternoon. My name is _____ and I'm calling from the Parramatta public health unit in Sydney. I was hoping to speak with the parents/guardian of _____. I am calling in regards to your child being at the emergency department at the Children's Hospital at Westmead in May. Records from the emergency department indicate _____ was present on 11th May. A number of children who were at the ED on the same day as _____ became infected with measles. We are trying to investigate the source of infection and whether there might have been other children who became infected with measles. We would like to ask you a few questions, it should take approximately ten minutes to complete. All the information we collect is confidential and only authorised public health staff will have access to this information. Would it be possible for you to answer our questions?"*

* If parent/guardian unavailable, ask what is the best time to call back.

Verbal consent given for interview:

Yes ☐

No ☐

**SECTION 2: PERSONAL DETAILS**

Age: ☐☐

Address: _____

Immunisation status (measles): _____

Number/s and age/s of sibling/s:

*"Does _____ attend childcare/preschool?"*

☐ Yes ☐ No If yes, where (name)? _____

**SECTION 3: HEALTH INFORMATION**

*"How is he/she going?"*

*"How long was _____ unwell for after being discharged from hospital?"*

*"Did the doctor prescribe any medicine upon discharge?"*

☐ Yes ☐ No

*"If yes, what medicines?"*

*"Did he/she get better after taking the medicine?"*

☐ Yes ☐ No ☐ Unsure

*"Did _____ get any new symptoms after being discharged from hospital?"*

☐ Yes ☐ No ☐ Unsure

*"If yes, could you please describe the symptoms?"*

*"How long did these symptoms last for?"*

*"Did you take him/her to see a doctor or need to return to hospital following his/her ED visit?"*

☐ Yes ☐ No ☐ Unsure

*"If yes, which doctor/hospital?"*

*"Prior to his/her visit on 11th May, did you visit any other doctor's surgeries or hospital?"*

☐ Yes ☐ No ☐ Unsure

*"If yes, which doctor/hospital?"*

---

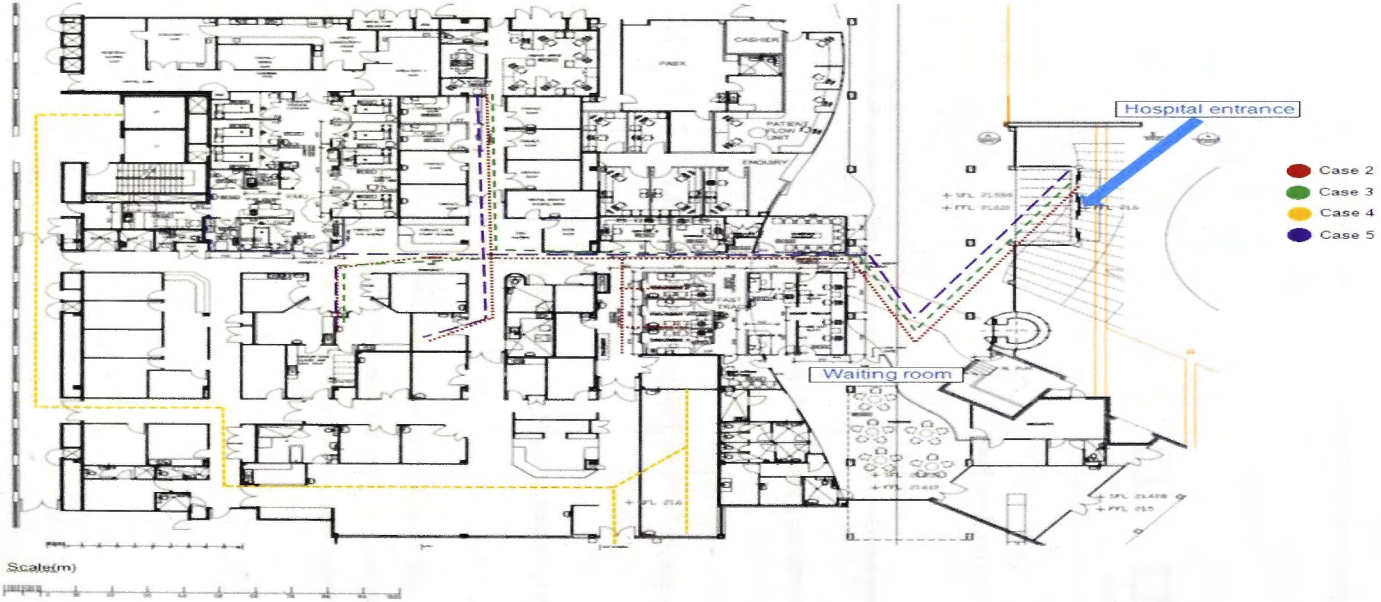
**SECTION 3: POTENTIAL EXPOSURE INFORMATION**

*"How long you were in the hospital for on the 11th May?"*

*"How long did you wait in the ED waiting room?"*

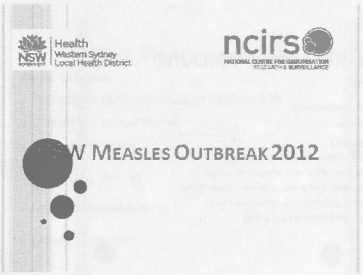
*"Thanks for your time to day, would you mind if we contacted you in the future to clarifying anything else? Please do not hesitate to contact the infectious disease control team at the Parramatta public health unit on 9840 3603 if you have any questions."*

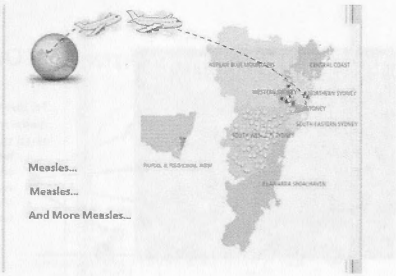
## Appendix 3.B. CHW ED and movements of measles cases, 11 May 2012

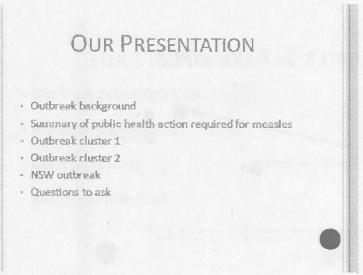


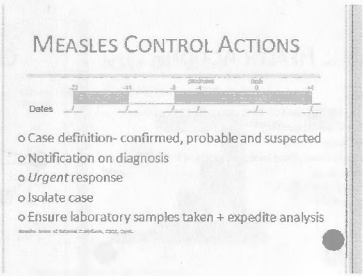
## Appendix 3.C. Presentation delivered to NCIRS Journal Club and to CHW Infectious Disease Meeting, November 2012

**Presentation drafted and delivered by Dr Shopna Bag, Ms May Chiew and Ms Alexis Pillsbury**



## Measles Control Actions

- Define *Infectious* period 4 days prior - 4 days after rash
- Define *Exposure* period 7 - 18 days prior to fewer onset
- Identify contacts Hospital, GP surgery, schools, childcare
  **All those in the same room and for 2 hours after[1]**
- 'Susceptible' contacts
  - Born after 1966, with
  - No documented evidence of receiving 2 doses of measles-containing vaccine, or
  - No documented evidence of immunity or laboratory evidence of prior measles

[1]Measles Series of National Guidelines, 2008, DoHA.

## Public Health Actions

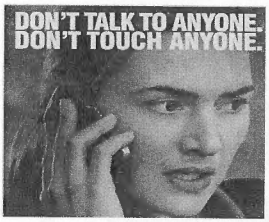
Actions for contacts:

- Provide information – exposure, symptoms, importance of calling ahead prior to seeking medical attention, isolation
- Post-exposure prophylaxis

  Within 72 hours
  MMR vaccine
  C/indicated: pregnancy, immunosuppression
  Within 3-6 days
  Normal Human Immunoglobulin, 0.2ml/kg
  For immunosuppressed contacts, 0.5ml/kg

**PEP-Overall 83% (27-96%) effective in preventing measles[1]**

1. Atkinson, Salmon, Zuckerman




## Outbreak Background

PB, 25yo Caucasian male

Australian-born

BH ED 13/4/2012

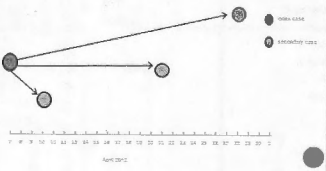
- Returned from Thailand 2 weeks ago
- Sore throat, itchy eyes, productive cough
- Widespread rash chest, abdomen, upper limbs
- Measles IgM detected, IgG not detected
- Case stated vaccinated as a child

## Public Health Actions

For this case:

- Contacts in Blacktown ED + GP (2 visits) =84 + 17 inpatients
- Family + friends at party =32
- (Soccer team)
- Travel companions (?long incubation period) = 7
- NHIG supplied=5
- MMR recommended=20
- Letters sent=13

## Cluster 1- April 2012



## Issues Identified

- Young adult index case- returned traveller
- Multiple presentations
- Isolation procedures
- Contact tracing
- 1 infant (9mo) secondary case
- 2 young adult (22 and 34yo) secondary cases

## Cluster 2

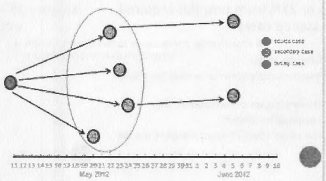
- SZ 11mo female
  CHW ED 23/05/2012, 25/05/2012
  Fever, cyanosis (23/05) and rash (25/05)
- WL 9mo female
  Medical Centre 24/05/2012
  Fever and cough (24/05)
- JJ 8mo male
  CHW ED 23/05/2012, 26/05/2012, 27/05/2012
  Testicular pain(23/05), fever (26/05) and rash (27/05)
- RC 17yo female
  Medical Centre 24/05/2012, 28/05/2012
  Fever, cough, conjunctivitis and rash(24/05)

## Public Health Action

For the four cases:

- Contacts in CHW ED/ Medical Centres=270
- Contacts at school formal
- Contacts at school
- NHIG supplied= 18
- MMR recommended= 8
- Letters sent= 100

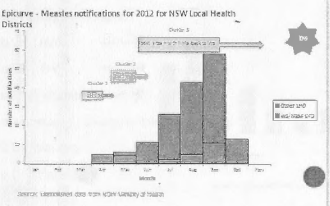
## Cluster 2- May 2012

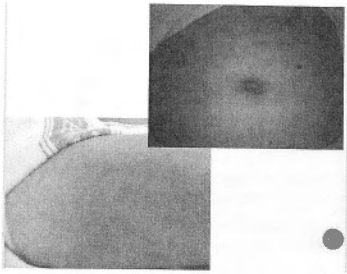



## Issues Identified

- Multiple presentations
- Infants < 12 months
- Contact tracing
- Source of infection

## NSW Outbreak





## 'Measles...a Heat-Seeking Missile'
-P. McIntyre

- TARGET: Healthcare setting weaknesses
- TARGET: Population immunity weaknesses

## Healthcare Setting Weaknesses

- Of NSW outbreak cases through Sept 2012:

29 cases or 27% were hospital-acquired from 11 source cases

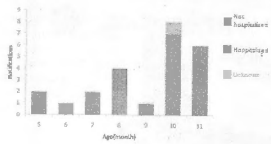
Of those 11 source cases:

- 81% presented multiple times to various healthcare facilities
- None was isolated upon presentation/triage
- 45% were eventually isolated
- Median time til isolation: 21 hours (range: 8 hrs -32 hrs)

## Population Immunity Weaknesses

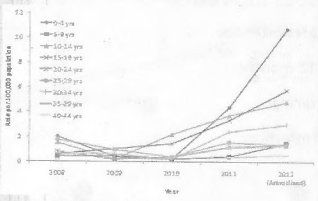
- Of the NSW outbreak cases through Sept 2012:
  - 22% infants
  - 25% Pacific Island descent and 4% Aboriginal descent (of NSW cases only)
  - 12% young adults (age 30-34 year olds)
  - ?? Vaccinated??

## Infant measles notifications <1, by hospitalisation status, NSW, 2012



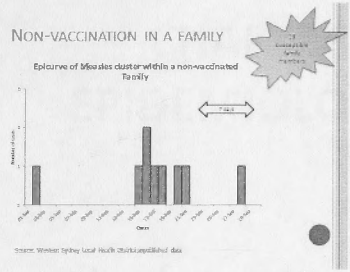

Source: Unpublished data from NSW Ministry of Health

## NSW measles notification rates by age group, 2008- Sept 2012




Source: Unpublished data from NSW Ministry of Health

## Non-vaccination in a family




Source: Western Sydney Local Health District unpublished data

## Questions to Ask

- Re: Healthcare facilities and transmission:
  - Why aren't we identifying measles?
  - Why are patients presenting multiple times to multiple healthcare facilities?
  - Are existing isolation procedures and facilities appropriate/effective?

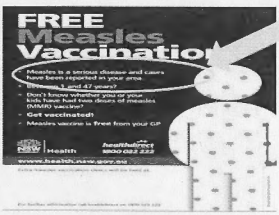
## Questions to Ask

- Re: High-risk groups:
  - How can we improve protection for infants <12mo?
  - How do we increase vaccine uptake in young adults?
  - How do we improve vaccine uptake and awareness in Pacific Islander communities?
  - ?? Vaccine objectors??

## Questions to Ask

- Re: resources:
  - How much time, human resources and money should we expend to stop measles outbreaks?

## Answers?




## Acknowledgements


- Dr Vicky Sheppeard
- WS LHD
- SSW LHD
- NSW Ministry of Health
- Associate Professor Kristine Macartney
- Dr Aditi Dey
- Dr Helen Quinn

# CHAPTER 4. APPLIED EPIDEMIOLOGICAL PROJECT

## Aspects of measles epidémiology in an era of elimination

# TABLE OF CONTENTS

# PREFACE

## Background and scope of the chapter

Certain characteristics of recent measles outbreaks in Australia and other developed countries have been indicative of the changing epidemiology of measles in an era of elimination. In countries where elimination has been achieved, cases are rare and typically imported either by travellers or immigrants from countries where indigenous transmission still occurs and vaccination coverage is low. Another problematic demographic consists of young adults who may have missed out on vaccination.

These characteristics were epitomised by the New South Wales (NSW) 2012 outbreak, described in detail in Chapter 3. The index case was an Australian-born young adult aged 25 years who likely missed out on the school-based catch-up component of the Measles Control Campaign launched in 1998. Of the ensuing outbreak cases, a large number occurred among those aged 20–59 years, and a surprisingly high proportion was aged 10–19 years. Most of these were unvaccinated or were unsure of their vaccination status. Moreover, a disproportionate number of total outbreak cases, as well as those cases aged 10–19 years, were individuals of Pacific Islander descent.

Another common characteristic in this era of measles elimination—when cases are rare and painstaking efforts are made to trace all possible lines of transmission—has been the frequent identification of healthcare settings as the loci of measles transmission. The reasons these transmissions occur are well understood. With the relative rarity of measles, and its symptoms being somewhat non-specific, presentations to healthcare facilities are often missed, and failure to isolate cases efficiently and effectively has contributed to the propagation of outbreaks. The NSW 2012 outbreak proved a case in point; healthcare transmissions were common, as was the high number of infants aged <1 year infected at a healthcare facility.

This chapter consists of two separate sections. While standing alone, they are united by their common theme of measles in an elimination era. Part One presents vaccine effectiveness analyses conducted for the NSW 2012 outbreak and for national

notifications from 2006–2012. Part Two consists of an analysis of the role of healthcare setting transmissions in perpetuating the 2012 outbreak.

The beginning pieces of this chapter (Preface; Abbreviations; List of Tables; List of Figures) refer to both Part One and Part Two of this chapter. They are then presented as stand-alone reports with individual abstracts. References included at the end of the chapter are for both Parts combined.

## Investigatory role

Though I primarily assisted Western Sydney with the measles outbreak response, I also cleaned and entered case data for the Sydney South Western Public Health Unit (PHU). Moreover, when the NSW Ministry of Health assumed coordination of the outbreak response, I assisted the Communicable Disease Branch with epidemiological analysis of the outbreak with a focus on healthcare setting transmissions. While doing so, I drafted a briefing report updating the NSW Measles Expert Working Group on healthcare setting transmissions and the efficacy of the two hour contact tracing rule. This work provided the initial foundation for a presentation which I delivered at the 2013 joint Communicable Disease Control (CDC) and Australasian Society for Infectious Diseases (ASID) Conference in Canberra in March 2013.

This work then developed into the collaboratively written draft paper, included in Part Two of this chapter. The draft was written by my Master of Philosophy Applied Epidemiology (MAE) and National Centre for Immunisation Research and Surveillance (NCIRS) colleague Ms May Chiew (first author) and me (second author). To date, we have contributed equally to the draft. Other co-authors included Dr Shopna Bag, Ms Kirsty Hope, Ms Sophie Norton, Dr Stephen Conaty, Dr Vicky Sheppeard and Professor Peter McIntyre. The draft will be submitted to the Western Pacific Surveillance and Response (WPSAR) Journal in 2014.

To conclude the measles-related work I had undertaken during my MAE, I decided to conduct vaccine effectiveness (VE) analyses for the NSW outbreak and for national notifications for the period 2006–2012. With guidance from Dr Helen Quinn—who also

assisted by extracting controls from the Australian Childhood Immunisation Register (ACIR) for the case-control component using an NCIRS SAS program—I compiled, cleaned and analysed the data and wrote the report which is included in Part One of this chapter.

## Lessons learned

The impetus for my healthcare setting transmission work arose from my time spent participating in the measles outbreak response effort. Participating in the response effort firstly at the local level with the Western Sydney PHU, and then following the response effort as the outbreak grew and became managed by the NSW Ministry of Health, was a valuable experience. Spending time at the Ministry provided insight into responding to outbreaks at the state level.

The primary lessons learned, however, concerned data analysis. Analysing healthcare transmissions required compiling, cleaning and entering case information data from case interviews and medical records; organising the data into a useable state was messy and time-consuming. Interpreting these data was challenging. For example, the detail included for some cases was extensive while for others it was minimal. For some cases, self-reported vaccination status was accepted as proof of vaccination while for others it was not.

Finally, conducting the healthcare transmission analysis highlighted a lesson which was significant for this project as well as others. That lesson was the importance of honing in on the 'take home' messages of one's work and figuring out the best way to clearly present that information—and how doing this for an oral presentation differs from doing so for a written manuscript.

This was my first exposure to the different types of VE analyses and what is required to conduct each. Upon reviewing each method, I opted not to employ the screening method because I had access to reliable denominator data. For the screening method, VE is approximated by comparing the proportion of vaccinated individuals with disease to the proportion of vaccinated individuals in the general population. My VE analysis

which was conducted using attack rates for the NSW outbreak cohort therefore provided sounder results than the screening method would have. It may be useful, however, to conduct the screening method to serve as a sensitivity analysis for validation of my results.

In addition to the analysis I conducted using attack rates for the outbreak cohort, I was fortunate to be able to conduct a case-control study to estimate VE for national notifications. This involved extracting and matching controls and having to consider issues of confounding. Moreover, this analysis allowed me to utilise Stata for more advanced analysis incorporating conditional logistic regression. Finally, conducting VE analyses demonstrated the limitations of routinely collected surveillance data, with the incompleteness of vaccination status fields impacting upon my results. Having witnessed the files for many outbreak cases, however, I better understand the origins of NNDSS data and why data fields may be incomplete.

Lastly, both components of this chapter presented a useful opportunity for consolidating my epidemiological skills within the context of vaccine preventable disease (VPD) policy and practice, perfectly uniting my MAE learning with skills specific to my placement at NCIRS.

## Public health impact

To ensure effective measles control and prevention strategies, formulating them within the appropriate context is critical. For most developed countries, the context is that of elimination. With this in mind, this chapter aims broadly to highlight characteristics of measles in an era of elimination.

Part One consists of vaccine effectiveness analyses. Such analyses are critical components for evaluating vaccination schedules and bolstering vaccine confidence among members of the public and healthcare providers. More importantly, these analyses provide evidence that the measles-mumps-rubella (MMR) vaccine has been effective, while serving as reminders to focus efforts on improving vaccination coverage. For this reason, my report is being provided to the NSW Ministry of Health,

the Measles Elimination Working Party and the Measles Verification Committee.

Part Two is an analysis of the role of healthcare setting transmissions in the NSW 2012 outbreak. As noted earlier, healthcare facilities have persisted as common transmission settings in recent measles outbreaks in post-elimination countries. Understanding how and why this continues to occur is imperative for improving prevention and control policy and practice. My initial brief written for the NSW Measles Expert Working Group concluded the two hour contact tracing rule may not be efficient or necessary in this post-elimination era. Since the NSW outbreak, the NSW Ministry of Health has been reviewing the efficacy of the two hour contact tracing guideline. My brief has contributed to that review.

Finally, little has been published providing detailed accounts of healthcare transmissions in recent outbreaks; the report included in Part Two of this chapter (which will be submitted to the WPSAR Journal in 2014), and my presentation to the joint CDC and ASID Conference in March 2013 (Appendix 4.B), will go some way to rectifying this knowledge gap.

## Acknowledgements

Dr Quinn assisted with the vaccine effectiveness analyses by providing me with guidance and extracting controls for the case-control study. Both she and Dr Martyn Kirk provided valuable support and advice for both components of this chapter. Additionally, Dr Mahomed Patel provided invaluable guidance for the structure and objectives of the healthcare setting transmissions component, both my presentation and the report. I will never forget the importance of finding and communicating the 'so what' factor of my work.

As mentioned in Chapter 3, I am grateful to Dr Vicky Sheppeard for inviting me to participate in the measles outbreak response effort conducted by the Western Sydney PHU. For my time at the NSW Ministry of Health, I would like to thank Mr Alex Rosewell for his guidance and Dr Jeremy McAnulty for warmly including me as part of the team. Ms Kirsty Hope of the Sydney South Western PHU provided feedback and

assistance with the data analysis component of the healthcare transmission draft. I would also like to thank all other co-authors mentioned above who have contributed to the healthcare transmission draft. Additionally, I would like to thank Dr Shopna Bag for presenting my CDC presentation on my behalf to the annual NSW Ministry of Health Communicable Disease Branch workshop in November 2013.

Finally, I would like to acknowledge the Vaccine Preventable Diseases Surveillance Section, Health Emergency Management Branch, Office of Health Protection, Australian Government Department of Health (DOH) for data from the National Notifiable Diseases Surveillance System (NNDSS), and Medicare Australia, Department of Human Services, for ACIR data.

# ABBREVIATIONS

| | |
|---|---|
| **ABS** | Australian Bureau of Statistics |
| **ACIR** | Australian Childhood Immunisation Register |
| **ACT** | Australian Capital Territory |
| **ARU** | Attack Rate Unvaccinated |
| **ARV** | Attack Rate Vaccinated |
| **ASID** | Australasian Society for Infectious Diseases |
| **CDC** | Communicable Disease Control (Conference) |
| **CI** | Confidence Interval |
| **DOH** | Department of Health |
| **ED** | Emergency Department |
| **GP** | General Practice |
| **IgG** | Immunoglobulin G |
| **IgM** | Immunoglobulin M |
| **LHD** | Local Health District |
| **MAE** | Master of Philosophy Applied Epidemiology |
| **MMR** | Measles-Mumps-Rubella (Vaccine) |
| **MMRV** | Measles-Mumps-Rubella-Varicella (Vaccine) |
| **NCIRS** | National Centre for Immunisation Research & Surveillance |
| **NIP** | National Immunisation Program |

| | |
|---|---|
| **NNDSS** | National Notifiable Diseases Surveillance System |
| **NSW** | New South Wales |
| **OR** | Odds Ratio |
| **PHU** | Public Health Unit |
| **R** | Reproductive Number |
| **UNICEF** | United Nations Children's Fund |
| **VIDRL** | Victorian Infectious Diseases Reference Laboratory |
| **VPD** | Vaccine Preventable DIsease |
| **WHO** | World Health Organization |
| **WPSAR** | Western Pacific Surveillance & Response (Journal) |

# LIST OF TABLES

# LIST OF FIGURES

# PART ONE

# AN ASSESSMENT OF MEASLES VACCINE EFFECTIVENESS, AUSTRALIA, 2006–2012

# ABSTRACT


## Introduction

Outbreaks present opportunities to analyse vaccine effectiveness which is important for excluding vaccine failure as a contributing component to an outbreak. Such analyses are also critical contributions to maintaining public and provider confidence in vaccines. This report assesses vaccine effectiveness for the NSW 2012 measles outbreak. It also estimates vaccine effectiveness at the population level using national notifications from 2006–2012.

## Methods

Notification data for both the outbreak analysis and the population-based analysis were obtained from the NNDSS. Vaccination status was classified according to whether a case had received zero, one or two doses of measles containing vaccine. For both analyses, cases aged <1 year and those with unknown vaccination status were excluded. For the outbreak analysis, vaccine effectiveness was estimated for the two primary area health districts (South Western Sydney and Western Sydney) that were affected by the outbreak by calculating attack rates using population data from the NSW Government and vaccination coverage estimates from the ACIR. For the national analysis, all children with disease onset between 1 January 2006 and 31 December 2012 who were born after 1997 were included. These cases were matched to controls extracted from the ACIR according to date of birth and jurisdiction of residence. Vaccine effectiveness estimates were calculated based on dosage using odds ratios generated from employing conditional logistic regression.

## Results

For the outbreak cohort, vaccine effectiveness was estimated at 98.6% (95% Confidence Interval (CI): 98.1–99.0%) and 97.6% (95% CI: 95.2–98.8%) for one dose for South Western Sydney and Western Sydney respectively. For at least one dose, vaccine effectiveness was estimated at 98.5% (95% CI: 97.9–99.0%) for South Western Sydney and 96.9% (95% CI: 94.1–98.4%) for Western Sydney. In the population-based analysis,

vaccine effectiveness was estimated at 96.7% (95% CI: 94.5–98.0%) for one dose compared with zero doses and 99.7% (95% CI: 99.2–99.9%) for two doses compared with zero doses. For at least one dose, effectiveness was estimated at 98.7% (95% CI: 97.9–99.2%) compared with zero doses.

## Conclusion

Vaccine effectiveness estimates suggest that the vaccine was adequate to protect against measles infection in both the NSW 2012 outbreak and at the population level from 2006–2012 as revealed by the case-control analysis. Consequently, it is vaccination coverage gaps which present the serious barrier to Australia's maintaining and ratifying measles elimination status.

# AN ASSESSMENT OF MEASLES VACCINE EFFECTIVENESS, AUSTRALIA, 2006–2012

**Ms Alexis Pillsbury**[1,2], Master of Philosophy (Applied Epidemiology) Scholar

Dr Helen Quinn[1,3], Research Fellow

Affiliation(s)

1. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), The Children's Hospital at Westmead and the University of Sydney, New South Wales, Australia.
2. National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia.
3. Discipline of Paediatrics and Child Health, University of Sydney, The Children's Hospital at Westmead, Westmead, New South Wales 2145, Australia.

# INTRODUCTION

In 2012 Australia experienced its largest measles outbreak since 1997. Commencing in NSW in April with an imported case in a 25 year old Australian traveller, the outbreak persisted through November, resulting in 168 notified cases.

The National Immunisation Program (NIP) has funded the MMR vaccine since the late 1980s, with two doses recommended since 1992. As part of the effort to eliminate measles, various funded catch-up campaigns have attempted to ensure that anyone born since the 1970s has received two doses of measles containing vaccine; anyone born since 1966 has been recommended receipt of two doses.[1] The second dose has been scheduled for 4 years of age since 2000, although this has recently changed to 18 months of age commencing in July 2013 with the introduction of the measles-mumps-rubella-varicella (MMRV) vaccine.[2, 3]

Though efforts to eliminate measles have resulted in a notable decrease in notifications since the mid-1990s, vaccination coverage rates hover below 95% which is considered optimal for herd immunity to protect against outbreaks.[4] Consequently, imported cases continue to trigger outbreaks like the one that occurred in NSW in 2012.

Outbreaks provide ideal opportunities to assess vaccine effectiveness; such assessments are important for determining whether or not an outbreak was due to vaccine failure or failure to vaccinate. Few measles vaccine effectiveness analyses have been published in Australia since the Measles Control Campaign of the late 1990s, with the exception of one that assessed vaccine effectiveness following a 2006 outbreak in NSW.[5]

This report assesses vaccine effectiveness for the NSW 2012 outbreak and at the population level between 2006–2012. Epidemiological trends for measles cases are also described.

# METHODS

## NSW outbreak

### *Case definition and case ascertainment*

Measles is required by legislation to be notified in all Australian states and territories using the national notifiable diseases case definition which stipulates that both probable and confirmed cases should be notified to public health authorities.[6] A confirmed case requires laboratory definitive evidence or a combination of clinical and epidemiological evidence. A probable case requires laboratory suggestive evidence and clinical evidence (Table 4.1).

**Table 4.1. National case definition for measles notifications**[6]

| | |
|---|---|
| Confirmed case | |
| Laboratory definitive evidence (one of the following) | |
| | Isolation of measles virus OR |
| | Detection of measles virus by nucleic acid testing OR |
| | Detection of measles virus antigen OR |
| | Immunoglobulin G (IgG) seroconversion or a significant increase in antibody level or a fourfold or greater rise in titre to measles virus EXCEPT if the case has received a measles-containing vaccine eight days to eight weeks before testing. (NOTE: paired sera must be tested in parallel) OR |
| | Detection of measles virus-specific IgM antibody confirmed in an approved reference laboratory EXCEPT if the case has received a measles-containing vaccine eight days to eight weeks before testing |
| Clinical evidence (all of the following) | |
| | A generalised maculopapular rash lasting three or more days AND |
| | Fever (at least 38° C if measured) at the time of rash onset AND |
| | Cough OR coryza OR conjunctivitis OR Koplik Spots |
| Epidemiological evidence | |
| | Contact between two people involving a plausible mode of transmission at a time when:<br>a. one of them is likely to be infectious (approximately five days before to four days after rash onset)<br>AND<br>b. the other has an illness that starts within seven to 18 (usually 10) days after this contact<br>AND<br>2. At least one case in the chain of epidemiologically linked cases (which may involve many cases) is laboratory confirmed |
| Probable case | |
| Laboratory suggestive evidence | |
| | Detection of measles specific IgM antibody other than by an approved reference laboratory EXCEPT if the case has received a measles-containing vaccine eight days to eight weeks before testing |
| Clinical evidence | |
| | As with confirmed cases |

Case investigation and public health response to the NSW 2012 outbreak adhered to the Australian national guidelines.[7] All confirmed cases with symptom onset date between 7 April and 29 November 2012, an epidemiological link to South Western Sydney or Western Sydney Local Health Districts (LHDs) where the majority of

outbreak cases occurred, with no history of recent overseas travel, and an unknown or D8 genotype were considered part of the outbreak. Any case lacking a clear epidemiological link to a confirmed outbreak case was genotyped at a reference laboratory. Where possible, vaccination status was validated using the ACIR. The ACIR is a population-based register which includes all children of citizens and permanent residents enrolled in the national publicly funded healthcare system, regardless of vaccination status (99% enrolment by 12 months of age[8]).

### *Vaccine effectiveness estimates*

Vaccination status was classified according to whether the case had received zero, one or two doses, or whether the case's vaccination status was unknown. Cases aged <1 year of age were excluded from vaccine effectiveness analysis because they were not eligible for vaccination according to the immunisation schedule. Cases with unknown vaccination status were also excluded. Any dose recorded as having been administered within two weeks prior to a diagnosis date was excluded from the analysis.

Cases were classified according to LHD and vaccine effectiveness was calculated for Western Sydney and South Western Sydney LHDs using the following formula[9]:

Vaccine effectiveness= (ARU-ARV)/ARU*100

ARU: Attack rate unvaccinated

ARV: Attack rate vaccinated

Attack rates per 100,000 population were calculated by applying LHD vaccination coverage estimates (personal communication, December 2013; Mr Brynley Hull, Epidemiologist, NCIRS) to LHD estimated resident population data.[10] Vaccine effectiveness was calculated for one dose and for at least one dose. Ninety-five percent CIs were calculated for the risk ratios generated from the formula above.

## Population-based analysis

### *Case definition and study population*

Measles cases were defined as outlined above according to the national definition. All measles cases notified to the NNDSS with an onset between 1 January 2006 and 31 December 2012 born after 1996 were included. Data were restricted to 2006–2012 because the completeness of vaccination status data included in the NNDSS for all states and territories was adequate from 2006. Because the ACIR began in 1996, it only contains children aged <17 years. Therefore, as controls were extracted from the ACIR and matched according to age, only cases aged <17 years were included in the analysis. Those aged <1 year were also excluded from analysis because they were not eligible for measles vaccination.

NCIRS holds a de-identified data set for the ACIR. For each case, controls were randomly sampled from the ACIR and matched to cases by date of birth +/- one day and state or territory of residence. As the analysis relies on discordance in vaccination status between cases and matched controls, and given the high vaccine coverage for one and two doses of measles-containing vaccines (93.9% at 24 months and 89.6% at 5 years)[4] and the ready availability of controls from the ACIR, 20 age-matched controls were sampled for each case to maximise precision.

Vaccination status for cases was obtained from the relevant NNDSS fields as recorded by each state and territory. Status was summarised as zero, one or two doses or unknown. Where the NNDSS had only classified a case as partially or fully vaccinated, this was interpreted according to the case's age and the vaccination schedule in place at the time of illness. Any dose which was recorded to have been administered within two weeks prior to diagnosis was excluded from analysis. Vaccination status for controls, as well as gender and Indigenous status, was obtained from the ACIR. Controls could not be included in the analysis if they had received a dose within 0–14 days prior to onset of illness in their matched case. Comparisons of characteristics between cases and controls were performed using the Pearson $\chi 2$ test and a

significance level of $p<0.05$.

### *Vaccine effectiveness estimates*

Cases and controls were ultimately analysed in Stata 12 after being matched using SAS 9.2 and exported between programs using Excel 2010. Conditional logistic regressions controlling for age and jurisdiction were conducted to estimate odds ratios (ORs) for receipt of one and two doses for cases compared with their matched controls. Logistic regression was also conducted to estimate ORs for cases receiving at least one dose compared with their matched controls. Vaccine effectiveness estimates and 95% CIs were then calculated based on the OR using the following formula[9]:

Vaccine effectiveness= (1-OR)*100

Ethics approval was not required for these vaccine effectiveness analyses as de-identified NNDSS and ACIR data are routinely provided to NCIRS for the purposes of disease surveillance as outlined in a funding agreement with the DOH.

## RESULTS

## NSW outbreak

### *Cohort characteristics*

Of the 168 total cases in the NSW 2012 outbreak, 92.9% (n=156) occurred in South Western and Western Sydney LHDs. Thirty-six (21.4%) of the total outbreak cases were infants too young to be vaccinated. Forty-nine (29.2%) cases occurred among those aged 10–19 years. Seventy-three of the 168 cases (43.5%) were reported as

unvaccinated; seven of these 73 had reportedly received vaccination during the exposure period and therefore these seven were classified as unvaccinated. Forty (23.8%) had unknown vaccination status. For those with unknown vaccination status, 72.5% were aged 20–59 years and 25.0% were aged 10–14 years. Only one case aged <10 years had unknown vaccination status. Figure 4.1 displays cases by age group and vaccination status.

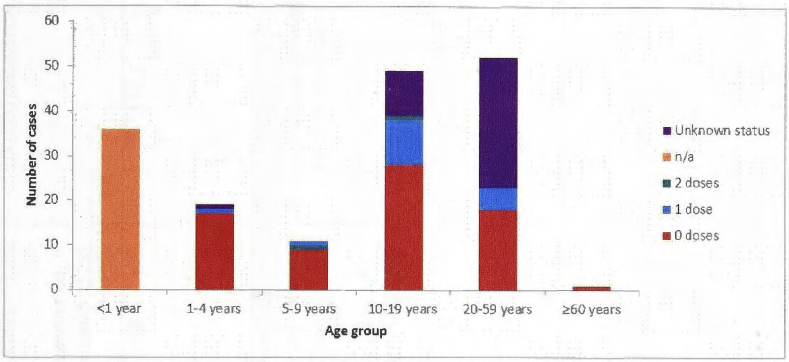



**Figure 4.1. Number of notified measles cases by age group and vaccination status, NSW outbreak, 2012**

### *Vaccine effectiveness estimates*

Of the 168 outbreak cases, 36 were excluded because they were infants aged <1 year who were too young for vaccination. Forty cases with unknown vaccination status were also excluded. Ninety-two cases remained eligible for the vaccine effectiveness analysis (Appendix 4.A).

Of these 92 cases, 73 were from South Western Sydney LHD and 16 from Western Sydney LHD. The estimated resident population for South Western Sydney LHD was 875,384; it was 846,174 for Western Sydney LHD. Estimated vaccination coverage (one dose) was 94.0% and 93.7% for South Western Sydney and Western Sydney LHDs respectively.

Vaccine effectiveness for each LHD for one dose and at least one dose is detailed in Table 4.2. For both districts, all estimates ranged between 96.9% and 98.6%.

**Table 4.2. Measles attack rates per 100,000 population and estimated MMR vaccine effectiveness by dosage, South Western and Western Sydney LHDs, 2012**

| South Western Sydney LHD | | | | | |
|---|---|---|---|---|---|
| | Number vaccinated cases (vaccinated population=822,860) | Attack rate vaccinated per 100,000 population | Number unvaccinated cases (unvaccinated population=52,523) | Attack rate unvaccinated per 100,000 population | Vaccine effectiveness (95% Confidence Interval) |
| One dose | 13 | 1.6 | 59 | 112.3 | 98.6% (98.1–99.0%) |
| At least one dose | 14 | 1.7 | | | 98.5% (97.9–98.9%) |
| **Western Sydney LHD** | | | | | |
| | Number vaccinated cases (vaccinated population=792,865) | Attack rate vaccinated per 100,000 population | Number unvaccinated cases (unvaccinated population=53,308) | Attack rate unvaccinated per 100,000 population | Vaccine effectiveness (95% Confidence Interval) |
| One dose | 4 | 0.5 | 11 | 20.6 | 97.6% (95.2–98.8%) |
| At least one dose | 5 | 0.6 | | | 96.9% (94.1–98.4%) |

## Population-based analysis

### *Secular trends among measles notifications*

Between 1995-2012, 4,111 measles notifications were reported to the NNDSS. Efforts to achieve and maintain measles elimination have resulted in a decrease in notifications in Australia since 1995 (Figure 4.2). In 1995, there were 1,182 notifications of measles in Australia. This decreased throughout the 1990s, and from 2000–2012, notifications ranged from 10–199 annually. Notifications from NSW (n=1,716) and Queensland (n=768)–two of Australia's most populous states–have comprised 60% of all notifications. Since 2000, a disproportionate amount of notifications has been for those aged 20–59 years. However, notifications in 2011–2012 also included an increase in cases aged 10–19 years. Most 2012 notifications were from the NSW outbreak and notable among those cases was the increase in notifications among infants <1 year of age who were too young to be vaccinated.

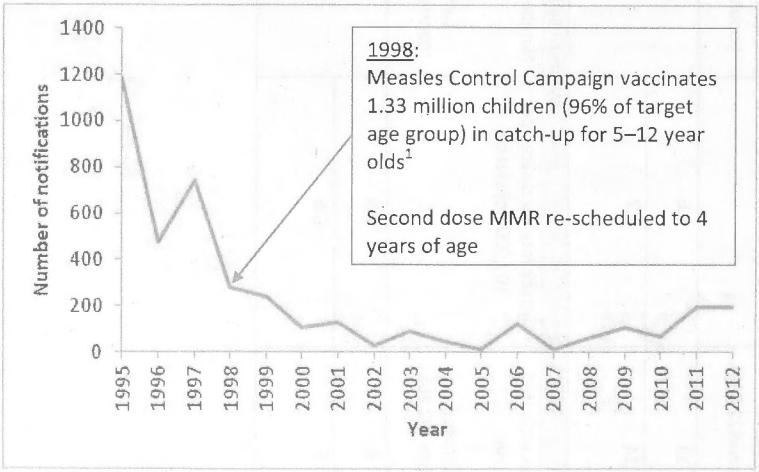



**Figure 4.2. Number of measles notifications, Australia, 1995–2012[2, 11]**

### *Vaccine effectiveness estimates*

After excluding all notifications with disease onset prior to 2006 and those with a date of birth prior to 1997 or aged <1 year at the time of illness, 207 notifications remained. The majority of these notifications (73.4%, n=152) were from NSW and Queensland. In terms of age, the majority of cases (40.1%, n=83) were aged 1–4 years; 30.4% (n=63) were aged 5–9 years and 29.5% (n=61) were aged 10–15 years.

Eighteen cases were excluded from the analysis due to their unknown vaccination status. More than half of the excluded cases (55.5%, n=10) were aged 10–15 years. All but one excluded notification resided in either NSW or Victoria. Seven cases included in the analysis were classified as having received zero doses of vaccine because they had received a dose immediately after exposure. Ultimately, 189 cases were included in the vaccine effectiveness analysis (Appendix 4.A). Of these, 24.9% (n=47) were also cases included in the NSW outbreak analysis.

Twenty controls were extracted from the ACIR for each control, resulting in a total of 3,780 controls. There were no significant differences between cases and controls in terms of gender or Indigenous status (Table 4.3).

**Table 4.3. Characteristics of cases and controls included in the population-based measles vaccine effectiveness analysis**

| | | Cases (%) n=189 | Controls (%) n=3780 | p value |
|---|---|---|---|---|
| Gender | Male | 92 (48.7%) | 1,975 (52.2%) | 0.34 |
| | Female | 97 (51.3%) | 1,805 (47.8%) | |
| Indigenous status* | Indigenous | 8 (4.2%) | 200 (5.3%) | 0.52 |
| | Non-Indigenous | 161 (85.2%) | 3,171 (83.9%) | |
| Number of doses | 0 | 160 (84.7%) | 437 (11.6%) | <0.001 |
| | 1 | 22 (11.6%) | 1,403 (37.1%) | |
| | 2 | 7 (3.7%) | 1,940 (51.3%) | |

*20 cases and 409 controls had unknown Indigenous status.

The estimated vaccine effectiveness for one dose MMR was 96.7% (95% CI: 94.5–98.0%). For at least one dose, vaccine effectiveness was estimated to be 98.7% (95% CI: 97.9–99.2%) and for 2 doses it was 99.7% (95% CI: 99.2–99.9%).

## DISCUSSION

This analysis demonstrates that the measles vaccine has been effective and that vaccine failure did not cause the NSW outbreak. Vaccine effectiveness increased slightly by dose for the national analysis. Regarding the outbreak analysis, vaccine effectiveness was slightly higher for those residing in South Western Sydney as compared with Western Sydney, albeit with overlapping CIs. These vaccine effectiveness calculations were similar to that reported by Sheppeard *et al* following a

2006 NSW outbreak where employment of the screening method yielded 96% vaccine effectiveness.[5] Recent vaccine effectiveness analyses from other developed countries have also concluded similar effectiveness,[12-14] with the exception of a 2008 analysis of the population-wide outbreak in Ukraine which concluded 93.1% effectiveness for two doses.[15]

Though it was unlikely that poor vaccine effectiveness had played a part in contributing to measles transmission in Australia over the period of 2006–2012, it is nevertheless important to conduct such an analysis to rule out vaccine effectiveness as a contributing factor. This is a critical component of evaluating the immunisation schedule and any changes it has undergone. As Australia strives to maintain and ratify elimination status—broadly defined as the absence of transmission of endemic measles—[16] it is critical not only to understand why and how transmission continues to occur, but also to be able to document all evidence which explains current measles epidemiology. This vaccine effectiveness analysis is an important contribution to this evidence.

Selection and misclassification biases are known to affect vaccine effectiveness analyses. Specifically, problems with case definitions, case ascertainment and ascertainment of vaccination status may bias analysis.[17] Notification procedures and a standardised and sensitive case definition make it unlikely that many cases were missed, neither nationally notified nor NSW outbreak specific cases. Clinical features, high infectivity of the illness and the requirement for laboratory evidence for all probable as well as confirmed cases make it unlikely that cases will ultimately be misclassified.[18] Moreover, suspected cases found to not be measles are not reported to the NNDSS[19] and were not included in the NSW outbreak cohort.

Bias associated with vaccination status classification is likely the most serious limitation to this analysis. Vaccination status was obtained from the NNDSS data and reliant upon the information provided by each state and territory. While vaccination status is sometimes validated by medical records and ACIR data, often it is reliant upon self-reporting which may be subject to recall bias. Studies have demonstrated that parental recall of vaccination status may overestimate vaccination coverage, though

requirement for written verification may lead to underestimates.[20, 21] It is evident from reviewing notes from the NSW outbreak cases that sometimes self-reports were accepted as proof of vaccination and other times they were not. For the purposes of this analysis, vaccination status was accepted as whatever was reported in the relevant NNDSS field.

With 40 cases from the NSW outbreak analysis and 18 cases from population-based analysis excluded due to unknown vaccination status, it is evident that vaccination status data completeness in the NNDSS could be improved. Because there was a high proportion of cases with unknown vaccination status who were consequently excluded from the analyses,[9, 22] each of these analyses likely would have benefitted from sensitivity analyses assessing what the vaccine effectiveness estimates would have been if all those with unknown vaccination status had been included as unvaccinated cases or if all those with unknown vaccination status had been included as having received at least one dose of vaccine.

Admittedly, in this report, the high number of cases with unknown vaccination status may have been influenced by more than just incomplete NNDSS data. It has been suggested that the ACIR may underestimate coverage by 5% for both first and second doses of measles containing vaccines.[23] Moreover, incomplete ACIR records for older children who were included in the Register in its incipient years when reporting was not as robust may have contributed to the high proportion of cases with unknown vaccination status included in the population-based analysis. Again, sensitivity analyses may improve the validity of this work in light of this additional limitation.

It is likely that a proportion of those cases with unknown vaccination status among those included in the population-based analysis were of Pacific Islander background. Though no official NSW outbreak data are available summarising vaccination status by ethnicity, 36 cases in the outbreak were of Pacific Island descent, and of those, 29 (80.1%) were Samoan. Those of Pacific Islander background were overrepresented among outbreak cases aged 10–19 years.[24] Anecdotal evidence reported by Najjar *et al* suggest that South Western Sydney high school students of Pacific Islander background may have missed out on routine childhood vaccinations both before and after their

arrival in Australia.[24] Based on this knowledge of the outbreak cases, and given that most cases included in the population-based analysis were from Queensland and NSW—the states with the highest proportions of Samoan born populations[25]—it is reasonable to suggest that a proportion of cases with unknown vaccination status in the national notification data were likely of Pacific Islander background. Although vaccination coverage among Pacific Island nations varies,[26] World Health Organization (WHO)-UNICEF (United Nations Children's Fund) estimates of Samoan vaccination coverage from 2003–2011 range from 45–67%; it is only in 2012 that estimates appear higher at 85%.[26] Consequently, many of the cases with unknown vaccination status excluded from the population-based analysis may have been more likely to have been unvaccinated than vaccinated if they were indeed of Pacific Islander descent. This would have resulted in underestimated vaccine effectiveness. Admittedly, however, further research would be required to support the hypothesis that a proportion of those with unknown vaccination status were likely Pacific Islanders and therefore more likely to be unvaccinated.

The final limitation of this study which should be acknowledged is that, as with any vaccine effectiveness analysis, confounding may be problematic. To remove the potential for confounding, cases and controls were matched by date of birth and jurisdiction of residence. Cases and controls were not significantly different in regards to gender or Indigenous status.

Ruling out vaccine effectiveness as a contributing factor in recent transmission and outbreak events in Australia means that gaps in vaccination coverage remain problematic to achieving elimination. Nation-wide coverage estimates from 2010 report 93.9% MMR coverage for those aged 24 months (birth cohort 1 January–31 March 2011) and 89.1% for those aged 60 months, with NSW-specific coverage estimates at 93.8% and 89.3% for 24 months and 60 months of age respectively.[4] These percentages, however, conceal small pockets of lower coverage rates. The lowest 24 month coverage rates by Medicare Local catchment are recorded by North Coast NSW and Eastern Sydney at 89%. The lowest 60 month coverage rate is recorded in Eastern Sydney at 84%.[27] These coverage estimates fall well short of the 95% mark

which is what WHO guidelines state is required to achieve and maintain elimination.[19]

It has been suggested that measles elimination has been achieved in Australia.[19] Supportive of Australia's claim of achieving elimination,[19] serosurvey results have demonstrated an effective reproductive number (*R*) of <1, meaning that the average number of secondary cases produced by a typical case remains below the epidemic threshold and indigenous transmission has been eliminated.[28] A 2013 report by Wood *et al*, however, has noted that seropositivity has decreased since 1999 and that *R* could be approaching one.[29] If this proves true, this could mean major setbacks for Australia's elimination progress.

The 2012 NSW outbreak cohort has highlighted areas where coverage gaps exist, demonstrating that those aged 10–19 years (29.2%, n=40) and those of Pacific Islander descent (21.4%, n=36) comprised a high proportion of cases.[24] Those aged 10–19 years who were born in Australia should have received two doses of measles containing vaccine as part of the 1998 Measles Control Campaign which successfully vaccinated 96% of the targeted primary school age group.[1] Why coverage gaps exist among this group is therefore particularly puzzling. Nevertheless, both this risk group and that comprised of individuals of Pacific Islander descent require dedicated efforts to better understand the nature of the coverage gaps and to appropriately target efforts to improve vaccination uptake. Another area of concern particular to measles epidemiology in this era of elimination includes the high number of cases occurring among infants too young to be vaccinated. In the NSW outbreak, infants <1 year of age comprised 21.4% (n=36) of cases.[24] This may be indicative of early waning of maternal antibodies among this vulnerable age group and may become more problematic as more mothers are protected by vaccine-conferred immunity rather than having had measles illness.[30-33]

This analysis provides evidence that vaccination failure has not contributed to recent measles cases in Australia including those which were part of the NSW 2012 outbreak. Consequently, it provides additional evidence that vaccination coverage gaps remain problematic to Australia's goal of maintaining and ratifying elimination status. It thus serves as a reminder that these coverage gaps must be recognised and targeted for

improvement. Vaccine effectiveness analyses like this one are valuable contributions to maintaining public and provider confidence in vaccination programs—which is also critical to achieving Australia's goal of sustained measles elimination.

# PART TWO

# THE CHANGING EPIDEMIOLOGY OF MEASLES IN AN ERA OF ELIMINATION: LESSONS FROM HEALTHCARE SETTING TRANSMISSIONS DURING AN OUTBREAK IN AUSTRALIA, 2012

# ABSTRACT


## Introduction

In countries where measles elimination has occurred and cases are rare, transmissions in healthcare facilities persist, perpetuating outbreaks and presenting a challenge to achieving and maintaining elimination. In 2012, seven years after it was argued that measles elimination had been achieved in Australia, the country experienced its largest measles outbreak in 15 years. Indeed, a high proportion of cases in this outbreak were healthcare-acquired. The objective of this analysis was to highlight key characteristics of healthcare-acquired cases and to consider whether, in a post-elimination setting, measles epidemiology might have changed.

## Methods

A healthcare-acquired measles case (secondary case) was defined as a confirmed case April–November 2012 who had a coincident attendance with a measles-infected individual (source case) at a healthcare facility 7–18 days before symptom onset. We conducted descriptive analyses using case series data from the metropolitan Sydney region to examine demographic characteristics, including age, sex, vaccination status and time of presentation. The number of presentations, time of presentation, symptoms upon presentation and isolation information were obtained for source cases by case interview and review of health records. The number of contacts exposed to source cases was provided by health authorities upon completion of contact tracing efforts.

## Results

There were 36 cases of healthcare-acquired measles and 16 source cases (of which 14 could be identified). All source and secondary cases overlapped in time, and source cases, on average, presented three times to a healthcare facility before being diagnosed. Eighty-four percent of secondary cases acquired measles from a case with rash.

## Conclusion

The most recent measles outbreak in Australia has indicated that measles epidemiology post-elimination may differ to that during a period of measles control. Given that healthcare facilities are common settings for measles transmission in countries nearing or having reported elimination, understanding characteristics of healthcare setting transmissions can assist in effectively targeting prevention strategies.

# THE CHANGING EPIDEMIOLOGY OF MEASLES IN AN ERA OF ELIMINATION: LESSONS FROM HEALTHCARE SETTING TRANSMISSIONS OF MEASLES DURING AN OUTBREAK IN AUSTRALIA, 2012

Ms May Chiew[1,2], Master of Philosophy (Applied Epidemiology) Scholar

**Ms Alexis Pillsbury**[1,2], Master of Philosophy (Applied Epidemiology) Scholar

Dr Shopna Bag[1,5], Public Health Medicine Trainee

Ms Kirsty Hope[3], Public Health Epidemiologist

Ms Sophie Norton[4], Public Health Officer Trainee

Dr Stephen Conaty[4], Public Health Physician

Dr Vicky Sheppeard[4], Public Health Physician

Professor Peter McIntyre[1,5], Director

Affiliation(s)

1. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), The Children's Hospital at Westmead and the University of Sydney, New South Wales.
2. National Centre for Epidemiology and Population Health, The Australian National University, Australian Capital Territory.
3. South Western Sydney and Sydney Local Health Districts, Camperdown, New South Wales.
4. New South Wales Ministry of Health, North Sydney, New South Wales.
5. Western Sydney Local Health District, Parramatta, New South Wales.
6. Discipline of Paediatrics and Child Health, University of Sydney, The Children's Hospital at Westmead, Westmead, New South Wales.

**To be submitted to Western Pacific Surveillance and Response Journal in 2014**

# INTRODUCTION

Between 2003–2008, Australia, England and Wales claimed to have eliminated the indigenous transmission of measles.[19, 30] Despite this, all three countries have experienced a number of measles outbreaks in recent times.[31, 32] This includes Wales' largest measles outbreak in 18 years, affecting 1,325 individuals (at the time of writing).[33] For both England and Wales, a consequence of their large scale and persistent outbreaks has been the re-introduction of indigenous measles in 2008.[34] Australian outbreaks have remained comparably smaller and it is likely that measles elimination has been sustained despite the country's largest outbreak in 15 years occurring in 2012. The US, where measles elimination was declared in 2000,[35] has also witnessed recent outbreaks, with over 222 cases in 2011, its largest outbreak since 2006.[36, 37]

One key characteristic observed to have perpetuated the 2012 Australian outbreak was the numerous transmissions which occurred in healthcare settings. Indeed, healthcare facilities have been reported as a prominent setting for measles transmissions in countries where measles is rare or eliminated.[38, 39] Reasons for this are well documented and include the low suspicion of infection among clinicians unfamiliar with the disease. This is further exacerbated by the difficulties inherent in diagnosing an illness characterised by the non-differential symptoms shared by myriad conditions.[40] Additionally, measles is highly infectious, and busy, dense environments like hospital Emergency Departments (EDs) are optimal settings to propagate outbreaks.[38] Of concern is that immunocompromised patients who often frequent healthcare facilities, particularly hospitals, if infected, experience more severe disease outcomes than immunocompetent individuals.[39]

Although numerous measles outbreak reports have been published describing healthcare transmissions,[32, 41, 42] many of these reports lack detailed case demographics and transmission characteristics. For example, the 2012 outbreak in northwest England identified that nearly 30% of confirmed cases reported before March were exposed to a measles case in a healthcare setting[32] while a separate

publication about this same outbreak stated that failure to isolate suspected cases had resulted in 'a significant number' of secondary cases.[43] No further case or healthcare transmission details were provided in either of these two reports. Similarly, little is known about the epidemiology of measles transmissions in Australian healthcare settings, particularly in the context of measles elimination.

This can be problematic. It is this type of research which informs updates to measles control and prevention strategies. Without such evidence being published, guidelines may consequently be inappropriate for responding to measles in an elimination context. For example, because the measles virus has been demonstrated to remain viable in air for up to two hours in a controlled experiment,[44] Australian guidelines have recommended that all individuals present for up to two hours after a confirmed measles case has departed should be treated as exposed contacts. The research which informed what has become known as the 'two hour rule'[7], however, is out-dated and was published in an era when measles was still endemic. [45, 46] In an elimination era when cases are rare, adhering to the 'two hour rule' may be unnecessary and inefficient.

Because little has been published on the characteristics of healthcare transmissions during measles outbreaks, and because there is a need for this type of evidence to inform prevention strategies and policies appropriate to a post-elimination setting, the objective of this study was to describe key characteristics of the 2012 Australian outbreak. The three key characteristics described include: the nature of exposure and exposure times between source and secondary cases; the delay in diagnosis of measles among source cases; and the stage of measles infection when transmission typically occurred.

## METHODS

Case series data describing confirmed measles cases were obtained from metropolitan Sydney LHDs in NSW, Australia's most populous state, between April and November 2012. Western Sydney, where the majority of outbreak cases resided, is culturally diverse. A third of its 2 million population were born overseas and it also includes the largest urban population of Aboriginal and Torres Strait Islander people in the country.[47]

In line with national guidelines, a confirmed measles case required laboratory evidence or clinical signs of infection with an established epidemiological link.[6] Clinicians and laboratories are legislatively required to notify public health authorities of suspected and confirmed measles cases.[48]

All confirmed cases temporally and regionally similar to the index case with genotype D8 or unknown were considered as belonging to this outbreak. Genotyping of specimens was conducted at the Victorian Infectious Diseases Reference Laboratory (VIDRL).[7]

Health authorities interviewed cases using a standardised questionnaire to obtain demographic information (age, sex, ethnicity, and vaccination status), symptom onset date and movements during exposure and infectious periods. The exposure period was defined as 7–18 days prior to rash onset and the infectious period was defined as five days prior to and four days after rash onset.

Health authorities compiled details from electronic patient notes (including clinical history, movements in hospital, number of individuals exposed) if cases had presented to an ED 7–18 days preceding onset of symptoms during either the exposure or infectious period as defined above. For all ED cases, public health authorities obtained details regarding arrival, triage, time seen and discharge time from hospitals.

A healthcare facility was defined as any premises that delivered healthcare services including hospital EDs, inpatient wards and General Practice (GP) clinics. A healthcare-

acquired infection (secondary case) was a confirmed case between April and November 2012 who had a coincident attendance with a measles-infected individual (source case) at a healthcare facility 7–18 days before symptom onset. For the purposes of this analysis, the term 'transmission event' has been used to describe instances where source cases transmitted to secondary cases in a healthcare facility.

Analysis was conducted using Stata 12 to describe demographic characteristics of source and secondary cases. Overlap times of source and secondary cases during presentation at a healthcare facility were calculated for each transmission event.

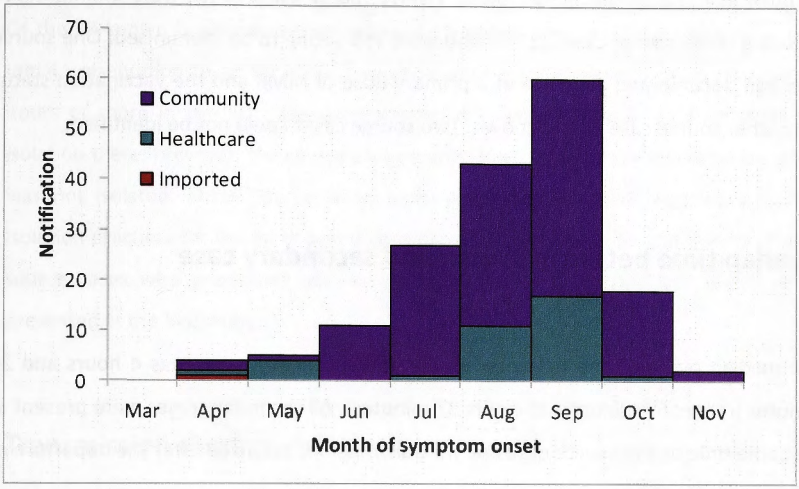
For source cases, proportions were calculated for type of healthcare facility of first presentation, number of presentations, number of cases isolated and symptoms during presentations. The average time spent by the source case in the healthcare facility was calculated. For each transmission event, a crude attack rate was calculated with number of individuals exposed used as the denominator. Crude attack rates were stratified by LHD to account for the different contact tracing procedures implemented by the districts.

Ethics approval was not required as this study was part of the public health response to the outbreak.

## RESULTS

There were 168 confirmed and 2 probable cases of measles, of which 36 (22%) were defined as healthcare-acquired (Figure 4.3).

**Figure 4.3. Number of confirmed and probable measles cases in the NSW outbreak by setting of transmission, April–November 2012**




## Healthcare-acquired (secondary) cases

The median age of the healthcare-acquired cases was 9 years (range: 5 months–37 years). Eleven cases (31%) were infants too young to be vaccinated, 16 cases (44%) were unvaccinated. One case (3%) had records of receiving two doses of MMR and three cases (8%) had received one dose of MMR. One case (3%) was a healthcare worker.

Thirty-three transmissions (33/36=92%) occurred in hospital, of which 29 transmissions (29/33=88%) occurred in an ED or ED waiting room and four transmissions (4/33=12%) in a ward. Three transmissions (3/36=8%) occurred at GP clinics.

## Source cases

The median age of known source cases (n=14) was 16 years (range: 7 months–39

years). Two source cases acquired measles in a healthcare setting and were also included as healthcare-acquired cases. Twelve source cases (86%) were unimmunised including three source cases (21%) who were too young to be immunised. One source case had documented evidence of a primary dose of MMR and the vaccination status of another source case was unknown. Two source cases could not be identified.

## Overlap time between source and secondary case

The median overlap time between source and secondary cases was 4 hours and 24 minutes (range: 59 minutes–35 hours 31 minutes). All secondary cases were present at the same time as the source case and no transmissions occurred after the departure of the source case.

Of the known source cases that transmitted infection in GP clinics, presentation and departure times of patients were not recorded. However, one of the three secondary cases that was acquired in a GP reported that a measles case was known to be present during their attendance at the GP. There were two transmission events which were triggered by unknown source cases resulting in four secondary cases for the first transmission event and one secondary case for the second. The four secondary cases resulting from the first transmission event all overlapped with each other by time and place. The one secondary case which resulted from the second unknown source case overlapped in time with three possible known source cases.

## Delay in diagnosis

On average, source cases presented three times to a healthcare facility before being suspected of measles. The median number of days from symptom onset to notification was 5 (range: 2–23) days and the median number of days from rash onset to notification was 2 (range: 0–18) days. A total of 1,251 contacts were exposed to

measles in healthcare facilities from the 14 known source cases.

Of the 38 known healthcare presentations by a source case, isolation occurred upon initial presentation to an ED once. Two other source cases were isolated after eight hours or more in the ED. One presentation of a source case to a GP resulted in isolation there; however, the source case re-presented at an ED on the same day and was not isolated. Three source cases were isolated upon admittance to a ward. Isolation practices for the 14 known source cases did not appear to improve for those source cases who presented later in the outbreak as compared with those who presented at the beginning.

### Transmission characteristics

Of the known source cases, a total of 38 presentations to a healthcare facility occurred. Eighteen presentations occurred prior to rash onset and led to 5 transmissions. Twenty presentations occurred following rash onset and resulted in 25 transmissions. Seventeen percent (n=6) of secondary cases acquired measles from a case without rash compared to 83% (n=30) of secondary cases who acquired measles from a case with rash.

In Western Sydney LHD, the crude attack rate for measles was 0.8% if the source case had no rash compared to 0.4% when the source case had a rash. In South Western Sydney LHD, the crude attack rate for measles was 5.1% if the source case had no rash compared to 11.0% if the source case had a rash.

## DISCUSSION

A key driver of NSW 2012 measles outbreak was numerous healthcare setting transmissions which occurred in part because of delayed diagnosis and

implementation of control procedures. Key characteristics of healthcare-acquired transmissions during the 2012 outbreak—the largest in Australia since 1997—have prompted health officials to reconsider public health response practices during measles outbreaks. Indeed, the results of this study suggest that a re-assessment of current knowledge in measles epidemiology is required, specifically how epidemiology may be different in an elimination context.

## Contact tracing and the 'two hour rule'

The value of contact tracing individuals up to two hours after an infectious case has departed a healthcare facility is questionable. Australia's two hour contact tracing rule appears to have been based on research published during the 1960s–1980s. Under experimental conditions, measles virus was found to persist in air for up to two hours.[44] This was further supported by airborne transmission occurring up to two hours after an infectious case departed on a number of occasions.[45, 46, 49] The number of transmissions from these reports, however, was low, at a total of six secondary cases,[45, 46, 49, 50] and all reports were published in the US at a time when measles was endemic, which would make identifying the source of infection challenging. Moreover, many of these reports described source cases who were vigorously coughing and likely to be 'superspreaders'.[45, 46] Reviews on nosocomial measles transmissions continue to use these out-dated sources as evidence of the virus persisting in air for up to two hours.[38, 39]

Among the known source cases in this study, no transmissions were observed to occur outside the direct time of exposure between the source case and susceptible individual in the healthcare setting. Although the overlap times between source and secondary case were missing for eight transmissions, anecdotal evidence purports that an overlap time existed for one of these transmissions while another transmission had three possible source cases, all of whom overlapped in time with the secondary case. The overlap time for the remaining six transmissions cannot be precisely ascertained. Four

of these were infected at the same time from an unknown source case. Though the source case remained unidentified, all four secondary cases overlapped succinctly in time and place. The final two cases with unknown overlap times were infected at GP clinics for which we were unable to obtain precise patient time and location detail.

A potential limitation to our analysis, however, was the differing contract tracing procedures used by LHDs in Sydney. One LHD contact traced according to the recommended 'two hour rule' while another contact traced up to 15 minutes after the infectious case departed the healthcare facility .

Nevertheless, based on our results, we believe sufficient evidence exists to question the necessity of the 'two hour rule'. Reports from a 2011 outbreak in Australia made a similar conclusion after finding all source and secondary cases had overlapped.[51] In England and Wales, only contacts with face-to-face exposure, exposure time excessive of 15 minutes or immunocompromised individuals with any contact (including over a short period after the measles case has departed) are followed up.[52]

If transmission does occur after a source case departs the exposure site, the secondary case would likely be captured by surveillance as measles is rare and Australia has a sensitive surveillance system. Thorough case investigation also ensures that all cases exposed by a confirmed case are likely to be identified. Consequently, the 'two hour rule' may be an inefficient and costly use of resources during times of an outbreak in this era of elimination. An Australian investigation into the costs associated with managing one measles case with 75 contacts in a 2011 outbreak estimated the expense at A$2,433.[53]

We recommend that a more targeted approach to contact tracing in Australia be adopted, particularly during outbreaks when time may be limited. Focusing only on individuals who were present at the same time as an infectious measles case in a healthcare setting would ideally minimise excess resource utilisation and be more appropriate for countries where measles is rare or eliminated.

## Infectious stage of measles

It has long been recognised that infectiousness of measles is greatest during prodrome[54] whereas the appearance of a rash indicates the beginning of viral clearance from blood and tissue.[55] In this study, however, a large proportion of healthcare transmissions appeared to occur after the rash onset of the source cases. Other reports have documented similar findings.[56, 57] This may suggest that infectiousness could be just as high during the rash stage of illness as during the prodromal stage. There are, however, a number of caveats to this interpretation, including the small number of transmission events, variable wait times and times of exposure for the secondary cases. Additionally, in our analysis, there was one source case who infected 11 secondary cases; this outlier may have skewed results. Nevertheless, attack rates were calculated by the number of individuals exposed at each presentation which may partially control for wait-times. It is unfortunate, however, that we were unable to obtain information on the number of susceptible individuals at each presentation to obtain more valid attack rates.

Moreover, our attack rates may be overestimates of the true attack rates. The denominator only included contacts of known source cases that transmitted measles in a healthcare setting. It excluded the healthcare contacts of measles cases who were infectious and presented to a healthcare facility but did not transmit infection. During this outbreak, there were 120 reported presentations (unpublished data) to a healthcare facility which did not result in any secondary transmissions. At the time of writing, however, the number of contacts from these presentations was unknown.

Despite these limitations, the observation that, for this study, more secondary cases acquired measles from source cases who had rashes than source cases who were in the prodromal stage of infection may serve as a reminder of the importance of increasing suspicion of patients presenting with rash during outbreaks.

A rash alone, however, is not the only predictor of infectiousness and more attention to the optimal environment for transmission to occur would be beneficial for

considering improvements to control efforts. It is likely a combination of viral load and vigorous coughing on the part of the source case combined with the length of exposure, physical layout of the exposure site, and the number of susceptible individuals present which contribute to wide-scale transmission events. Nevertheless, improved recording of clinical details of cases and suspected cases during times of outbreak may assist in improving our understanding of measles infectiousness.

## Delayed diagnosis

Delayed diagnosis and subsequent multiple presentations of measles cases were problematic during this outbreak and are common outbreak characteristics in countries where measles is rare.[39, 58] This contributes to the number of transmission events occurring within healthcare settings. A recent review found that up to 50% of cases in developed countries, particularly where measles elimination was established, had been acquired in a healthcare setting .[59]

At first presentation, only a low proportion of cases are suspected of having measles[60] because it is difficult to clinically distinguish from other viral systemic illnesses. A patient in the early stages of measles may present with a combination of non-differential symptoms, including fever and perhaps only one of the following: cough, coryza and conjunctivitis. Differential diagnoses include influenza and other common respiratory viral infections and allergic rhinitis. Even with the characteristic maculopapular rash, a measles diagnosis may be overlooked because of the disease's rareness and similarities to adeno- and enteroviral infection, other exanthems of childhood and drug allergy.[39, 56] Unable to obtain a successful diagnosis on first presentation, most source cases presented multiple times to both the same healthcare facility as their first presentation and to other healthcare facilities.

Although public health alerts were disseminated to healthcare facilities during this outbreak, including faxing and telephoning GPs in the worst affected areas, awareness did not appear to increase as the outbreak continued. Multiple healthcare

presentations by source cases were observed to occur even during the peak of the outbreak. More innovative approaches may be required to improve future control efforts, including establishing alerts that are triggered when 'fever' and 'rash' are entered into electronic medical records, however, such measures are yet to be evaluated.[61, 62]

Our results identified that even during the peak of the outbreak a number of measles cases who presented with rash were not suspected of having measles and subsequently were not isolated. Although a number of source cases was documented as having been isolated, isolation was enacted too late to prevent secondary transmission or isolation was ineffective. While isolation of an infectious case in a negative pressure room is the preferred method,[7] in many healthcare facilities this type of room is not available. A more feasible option may include confinement of a suspect case in a single private room with a face mask.[63] In busy EDs, however, single rooms may be scarce. In this outbreak, isolation practices were documented to have differed not only between hospitals but also within hospitals. Isolation practices may prove more effective if procedures are standardised and consistent.

Though several key limitations of this study have been detailed above, others are worth briefly noting. Though presentations by source cases to a healthcare facility may have been missed (eg, if the case presented at another GP/ ED) this is unlikely as cases were interviewed using a standardised questionnaire and cases are unlikely to forget seeking medical attention. There is a possibility that isolation of a suspected case could have occurred that was not captured in GP/ED medical records. If this detail was missing from medical records, however, the information would likely have been collected by public health authorities through communication with the attending clinician. Ultimately, if time and resources had permitted, it would have been ideal to compare the source cases who presented multiple times to a control group of individuals who were recognised immediately at a healthcare facility to determine if any risk factors led to misdiagnosis of measles. Such an approach may assist in better tailoring efforts to improve measles detection by clinicians during outbreaks.

# CONCLUSION

As more countries progress towards measles elimination, transmission in healthcare facilities assumes increasing importance as a remaining obstacle to improving measles control and prevention of outbreaks. Though imported measles cases will continue to challenge countries which have achieved elimination status, transmissions in healthcare facilities can surely be addressed more effectively to ensure that healthcare facilities are not contributing to outbreaks. Measles must remain high on the list of possible diagnoses when patients present with febrile rash. Diagnosis must be prompt and subsequent isolation appropriate. Observations from NSW 2012 outbreak suggest that these are areas which require improvement. Moreover, contact tracing procedures based on out-dated evidence may require revision to be better suited to the post-elimination context. Contact tracing all those who have been in the vicinity of the known case for up to two hours after the case departed may not be efficient or necessary in the elimination era. Instead, focussing on those who have had direct contact with a known case may be a more efficient use of resources. Continual strengthening of the evidence base with outbreak reports such as this may assist in improving our understanding of the pathogenicity and epidemiology of measles and consequently how best to target awareness as well as control and prevention efforts. Failing to do so may jeopardise the goal of maintaining and ratifying elimination status in Australia and elsewhere.

# REFERENCES


1. Turnbull FM, Burgess MA, McIntyre PB, Lambert SB, Gilbert GL, Gidding HF, et al. The Australian measles control campaign, 1998. Bull World Health Organ. 2001;79(9):882-8.

2. National Centre for Immunisation Research and Surveillance (NCIRS). Significant events in measles, mumps and rubella vaccination practice in Australia. [Internet] 2013 [cited 2013 December 28]; Available from: http://www.ncirs.edu.au/immunisation/history/Measles-mumps-rubella-history-December-2013.pdf.

3. Australian Technical Advisory Group on Immunisation (ATAGI). The Australian Immunisation Handbook. 10th ed. Canberra: Australian Government Department of Health and Ageing; 2013.

4. Hull B, Dey A, Menzies R, McIntyre P. Annual immunisation coverage report, 2010. Commun Dis Intell. 2013;37(1):E21-E39.

5. Sheppeard V, Forssman B, Ferson M, Moreira C, Campbell-Lloyd S, Dwyer D, et al. Vaccine failures and vaccine effectiveness in children during measles outbreaks in New South Wales, March-May 2006. Commun Dis Intell. 2009;33(1):21-6.

6. Australian Government Department of Health and Ageing. Australian national notifiable diseases case definitions: measles case definition. [Internet] 2004 [cited 2013 February 22]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_measl.htm.

7. Australian Government Department of Health and Ageing. Series of national guidelines. Measles. National guidelines for public health units. . 2009 [updated 19 February 2009; cited 2012 21 November]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/55AD336B864C7203CA25755F000307B6/$File/measles-song.pdf.

8. Hull BP, Deeks SL, McIntyre PB. The Australian Childhood Immunisation Register-A model for universal immunisation registers? Vaccine. 2009 Aug 13;27(37):5054-60.

9. Orenstein W, Bernier R, Dondero T, Hinman A, Marks J, Bart K, et al. Field evaluation of vaccine efficacy. Bull World Health Organ. 1985;65(6):1055-68.

10. NSW Government. Health statistics New South Wales: population growth by LHD. 2011 [cited 2014 February 4]; Available from: http://www.healthstats.nsw.gov.au/Indicator/dem_pop_lhnmap.

11. National Notifiable Diseases Surveillance System (NNDSS). Number of notifications of measles, received from state and territory health authorities in the period of 1991 to 2012 and year-to-date notifications for 2013. Canberra 2013.

12. Arenz S, Schmitt H, Tischer A, von Kries R. Effectiveness of measles vaccination after household exposure during a measles outbreak: a household contact study in Coburg, Bavaria. Pediatr Infect Dis J. 2005;24(8):697-9.

13. Wichmann O, Hellenbrand W, Sagebiel D, Satibanez S, Ahlemeyer G, Vogt G, et al. Large measles outbreak at a German public school, 2006. Pediatr Infect Dis J. 2007;26(9):782-6.

14. Yeung LF, Lurie P, Dayan G, Eduardo E, Britz PH, Redd SB, et al. A limited measles outbreak in a highly vaccinated US boarding school. Pediatrics. 2005 December 1, 2005;116(6):1287-91.

15. Velicko I, Muller L, Pebody R, Gergonne B, Aidyralieva C, Kostiuchenko N, et al. Nationwide measles epidemic in Ukraine: the effect of low vaccine effectiveness. Vaccine. 2008;26(52):6980-5.

16. World Health Organization Regional Office for the Western Pacific (WPRO). Field guidelines for measles elimination. Geneva 2004 [cited 2014 Janaury 2]. Available from: http://www.wpro.who.int/publications/docs/FieldGuidelines_for_MeaslesElimination_0F24.pdf.

17. Torvaldsen S, McIntyre P. Observational methods in epidemiologic assessment of vaccine effectiveness. Commun Dis Intell Q Rep. 2002;26(3):451-7.

18. Orenstein W, Hinman A, Papania M. Evolution of measles elimination strategies in the United States. J Infect Dis. 2004;189(Supplement 1):S17-S22.

19. Heywood A, Gidding HF, Riddell MA, McIntyre PB, MacIntyre CR, Kelly H. Elimination of endemic measles transmission in Australia. Bull World Health Organ.

2009;87:64-71.

20. Lister S, McIntyre P, Burgess M, O'Brien E. Immunisation coverage in Australian children: a systematic review. Commun Dis Intell. 1999;23:145-70.

21. Hawe P. Measles control: a best-practice challenge in public health. Aust J Public Health. 1994;18(3):241-3.

22. Orenstein W, Bernier R, Hinman A. Assessing vaccine efficacy in the field: further observations. Epidmiol Rev. 1988;10:212-41.

23. Hull B, Lawrence G, MacIntyre R, McIntyre P. Immunisation coverage in Australia corrected for under-reporting to the Australian Childhood Immunisation Register Aust N Z J Public Health. 2003;27:533-8.

24. Najjar Z, Hope K, Clark P, Nguyen O, Rosewell A, Conaty S. Sustained outbreak of measles in New South Wales, 2012: risks for measles elimination in Australia. Western Pac Surveill Response J. 2013;5(1):1-7.

25. Australian Government Department of Immigration and Citizenship. Community information summary: Samoa-born. 2011 [cited 2014 February 7]; Available from: http://www.google.com.au/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0CDoQFjAC&url=http%3A%2F%2Fwww.immi.gov.au%2Fmedia%2Fpublications%2Fstatistics%2Fcomm-summ%2F_pdf%2Fsamoa.pdf&ei=Ki70Uvm_O4mtkAWN5YHwAg&usg=AFQjCNFwKw3zm_xWKC_fDikCJZWAA3ciWg&sig2=IXlGtioKOoAi-1o6miML9A&bvm=bv.60983673,d.dGI.

26. World Health Organization (WHO). WHO vaccine-preventable diseases: monitoring system: 2013 global summary. 2014 [cited 2014 February 6]; Available from: http://apps.who.int/immunization_monitoring/globalsummary.

27. National Health Performance Authority. Healthy communities: immunisation rates for children in 2011-2012. Sydney2013.

28. Gidding H, Wood J, MacIntyre R, Kelly H, Lambert S, Gilbert G, et al. Sustained measles elimination in Australia and priorities for long term maintenance. Vaccine. 2007;25(18):3574-80.

29. Wood J, Heywood A, McIntyre P, MacIntyre R. Declining seropositivity in Australia and elimination status. Communicable Disease Control Conference; 2013 March 19-

20; Canberra, Australia 2013.

30. Ramsay ME, Jin L, White J, Litton P, Cohen B, Brown D. The elimination of indigenous measles transmission in England and Wales. J Infect Dis. 2003 May 15;187 Suppl 1:S198-207.

31. Wise J. Measles outbreak hits northeast England. BMJ. 2013;346:f662.

32. Vivancos R, Keenan A, Farmer S, Atkinson J, Coffey E, Dardamissis E, et al. An ongoing large outbreak of measles in Merseyside, England, January to June 2012. Euro surveillance. 2012;17(29).

33. Public Health Wales. Measles outbreak cases rise again as school vaccinations enter final week. [Internet] 2013; Available from: http://www.wales.nhs.uk/sitesplus/888/news/27327.

34. Measles once again endemic in the United Kingdom. Euro Surveill. 2008 Jul 3;13(27).

35. Katz SL, Hinman AR. Summary and conclusions: measles elimination meeting, 16-17 March 2000. J Infect Dis. 2004 May 1;189 Suppl 1:S43-7.

36. Parker AA, Staggs W, Dayan GH, Ortega-Sanchez IR, Rota PA, Lowe L, et al. Implications of a 2005 measles outbreak in Indiana for sustained elimination of measles in the United States. N Engl J Med. 2006 Aug 3;355(5):447-55.

37. Centers for Disease Control and Prevention (CDC). Measles - United States, 2011. MMWR Morb Mortal Wkly Rep. 2012 Apr 20;61:253-7.

38. Biellik RJ, Clements CJ. Strategies for minimizing nosocomial measles transmission. Bull World Health Organ. 1997;75(4):367-75.

39. Botelho-Nevers E, Gautret P, Biellik R, Brouqui P. Nosocomial transmission of measles: An updated review. Vaccine. 2012;30(27):3996-4001.

40. Durrheim DN, Kelly H, Ferson MJ, Featherstone D. Remaining measles challenges in Australia. Medical Journal of Australia. [Review]. 2007;187(3):181-4.

41. Sniadack DH, Mendoza-Aldana J, Jee Y, Bayutas B, Lorenzo-Mariano KM. Progress and challenges for measles elimination by 2012 in the Western Pacific Region. J Infect Dis. 2011 Jul;204 Suppl 1:S439-46.

42. Fielding JE. An outbreak of measles in Adelaide. Commun Dis Intell Q Rep. 2005;29(1):80-2.

43. Lamden KH, Vivancos R, McCann R, Ghebrehewet S. Why is measles so difficult? BMJ. 2013;346(f245).

44. De Jong JG, Winkler KC. SURVIVAL OF MEASLES VIRUS IN AIR. Nature. 1964 Mar 7;201:1054-5.

45. Remington PL, Hall WN, Davis IH, Herald A, Gunn RA. Airborne transmission of measles in a physician's office. JAMA. 1985 Mar 15;253(11):1574-7.

46. McIntyre PB, Gidding HF, Gilbert GL. Measles in an era of measles control. Med J Aust. 2000 Feb 7;172(3):103-4.

47. NSW Government. About Western Sydney: demographics. [Internet]; Available from: http://www.westernsydney.nsw.gov.au/about-western-sydney/demographics/.

48. New South Wales Government. Public Health Act 2010 No 127. [cited 2012 November 23]; online:[Available from: http://www.legislation.nsw.gov.au/viewtop/inforce/act+10+1991+FIRST+0+N/.

49. Sienko DG, Friedman C, McGee HB, Allen MJ, Simonsen WF, Wentworth BB, et al. A measles outbreak at university medical settings involving health care providers. Am J Public Health. 1987 Sep;77(9):1222-4.

50. Centers for Disease Control and Prevention (CDC). Measles--Hawaii. MMWR Morb Mortal Wkly Rep. 1984 Dec 21;33(50):702, 7-11.

51. Hope K, Boyd R, Conaty S, Maywood P. Measles transmission in health care waiting rooms: implications for public health response. Western Pac Surveill Response J. 2012 Oct;3(4):33-8.

52. Health Protection Agency. HPA National Measles Guidelines: local and regional services2010.

53. Flego K, Belshaw D, Sheppeard V, Weston K. Impact of a measles outbreak in Western Sydney on public health resources. Commun Dis Intell. 2013;IN PRESS.

54. Perry RT, Halsey NA. The clinical significance of measles: a review. J Infect Dis. 2004 May 1;189 Suppl 1:S4-16.

55. Griffin DE, Ward BJ, Esolen LM. Pathogenesis of measles virus infection: an hypothesis for altered immune responses. J Infect Dis. 1994 Nov;170 Suppl 1:S24-31.

56. WHO Regional Committee for the Western Pacific. Measles elimination, hepatitis B control and poliomyelitis eradication. Report of the regional committee summary

records of the plenary meetings. Manila 2005.

57. Sydney South Eastern Public Health Unit Infectious Diseases Team and Director. Outbreak report: measles cluster in south eastern Sydney with transmission in a general practice waiting room. Commun Dis Intell. 2001;25(1).

58. Sugerman DE, Barskey AE, Delea MG, Ortega-Sanchez IR, Bi D, Ralston KJ, et al. Measles outbreak in a highly vaccinated population, San Diego, 2008: role of the intentionally undervaccinated. Pediatrics. 2010 Apr;125(4):747-55.

59. Maltezou HC, Wicker S. Measles in health-care settings. Am J Infect Control. 2013 Jul;41(7):661-3.

60. Farrington CP, Grant AD. The distribution of time to extinction in subcritical branching processes: applications to outbreaks of infectious disease. J Appl Probab. 1999;36(3):771-9.

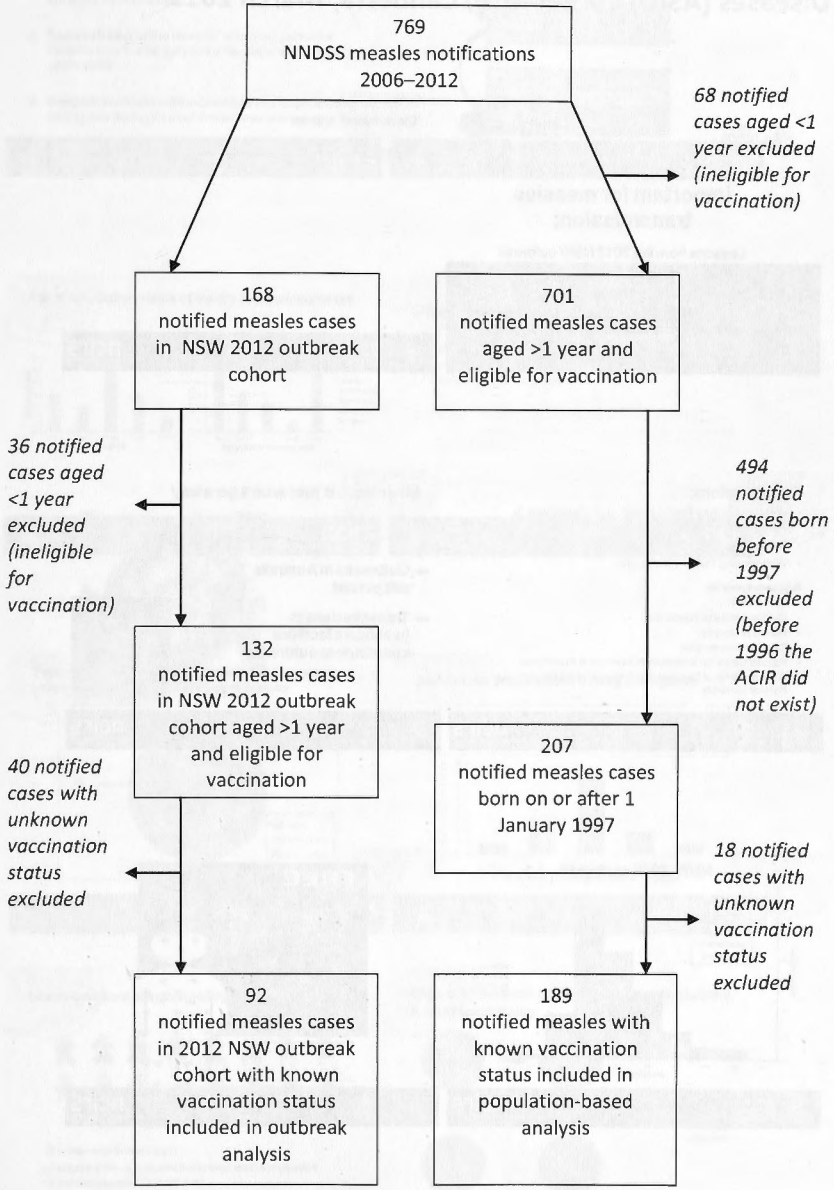
61. Lurio J, Morrison FP, Pichardo M, Berg R, Buck MD, Wu W, et al. Using electronic health record alerts to provide public health situational awareness to clinicians. J Am Med Inform Assoc. 2010 Mar-Apr;17(2):217-9.

62. Revere D, Nelson K, Thiede H, Duchin J, Stergachis A, Baseman J. Public health emergency preparedness and response communications with health care providers: a literature review. BMC Public Health. 2011;11:337.

63. Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. Am J Infect Control. 2007 Dec;35(10 Suppl 2):S65-164.

# APPENDICES

## Appendix 4.A. Flow diagram showing case selection for vaccine effectiveness analyses



## Appendix 4.B. Presentation delivered at joint Communicable Disease Control (CDC)/Australasian Society for Infectious Diseases (ASID) Conference, Canberra, March 2013*

Australian National University

ncirs

**The clinical setting is important for measles transmission:**

Lessons from the 2012 NSW outbreak

Alexis Pillsbury
Master of Philosophy (Applied Epidemiology) Scholar

Co-authors: May Chiew, Kirsty Hope, Shopna Bag, Sophie Norton, Stephen Conaty, Vicky Sheppeard, Peter McIntyre

**Disclosure of interest**

There are no conflicts of interest.

Australian National University ncirs

**Collaborators:**

- Western Sydney Public Health Unit, Parramatta & Penrith branches
- South West Sydney & Sydney Public Health Unit
- Wollongong Public Health Unit

**Acknowledgements:**

- NSW Health
- Children's Hospital Westmead
- Blacktown Hospital
- Campbelltown Hospital
- National Centre for Immunisation Research & Surveillance
- National Centre of Epidemiology & Population Health, Australian National University

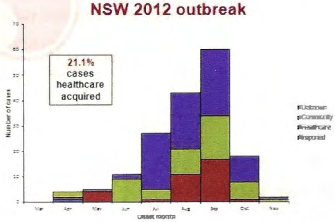
Australian National University ncirs

**Measles... it just won't go away**

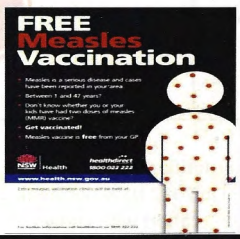
- Outbreaks in Australia still persist
- Transmissions in healthcare facilities contribute to outbreaks

Australian National University ncirs

**NSW 2012 outbreak**




Australian National University ncirs




ncirs

## Objectives

1. **Emphasise** that multiple undiagnosed presentations, delay in diagnosis & ineffective isolation contributed to the NSW 2012 outbreak
2. **Demonstrate** that the maximal infectious period for measles may not be the prodromal stage as commonly understood
3. **Support** reconsidering the need for the 2 hour contact tracing rule during times of limited resources

Australian National University ncirs

## Methods

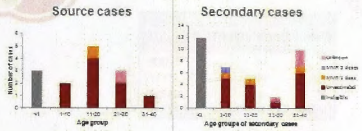
**Confirmed measles case:**
- Lab confirmation or
- Clinical signs of infection + epidemiological link
- April – Nov 2012

**Outbreak case:**
- NSW confirmed case
- Genotype D8 or unknown
- April – Nov 2012

**Secondary case:**
- Confirmed outbreak case with coincident attendance with a confirmed (source) case at a healthcare facility 7-18 days before symptom onset
- No known community epidemiological call links who could have infected

Australian National University ncirs

## Age & vaccination status of source & secondary cases



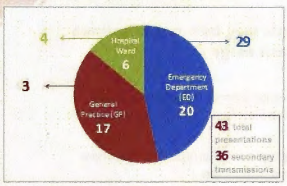

Australian National University ncirs


## Objectives

1. **Emphasise** that multiple undiagnosed presentations, delay in diagnosis & ineffective isolation contributed to the NSW 2012 outbreak
2. Demonstrate that the maximal infectious period for measles may not be the prodromal stage as commonly understood
3. Support reconsidering the need for the 2 hour contact tracing rule during times of limited resources

Australian National University ncirs


## Total number of healthcare presentations by source cases & resulting secondary transmissions

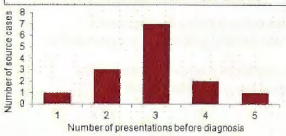



Australian National University ncirs

## Source case presentations & delay in diagnosis

Median days, symptom onset to notification: **5** (range: 2-23)

Median days, rash onset to notification: **2** (range: 0-18)




Australian National University ncirs

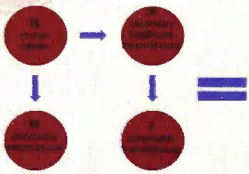
## Source cases not effectively isolated on presentation

No source case effectively isolated

- 2 isolated after 8+ hours in ED
- 1 isolated at GP– but departed & presented at ED & not isolated
- 2 isolated upon admittance to a ward
- 1 isolated upon initial presentation to an ED

Australian National University ncirs

## Impact of multiple undiagnosed presentations & diagnosis delay



**69/170** cases of 2012 NSW outbreak

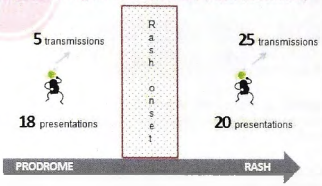
Australian National University ncirs

## Objectives

2. **Demonstrate** that the maximal infectious period for measles *may not* be the prodromal stage as commonly understood

Australian National University ncirs

## Source case stage of infectiousness when transmitted




Australian National University ncirs

## Objectives

3. **Support** reconsidering the need for the 2 hour contact tracing rule during times of limited resources

Australian National University ncirs

## Source & secondary case overlap times

| Secondary cases (n=36) | |
|---|---|
| Estimated overlap time (hours) with source case* | n (%) |
| 0-1 | 3 (10.7) |
| 1-2 | 2 (7.1) |
| ≥2 | 23 (82.1) |

*Unknown n=6

- All secondary cases overlapped in time with source case
- No secondary case infected after source case had departed
- Do we need 2 hour contact tracing rule?

Australian National University ncirs

## Conclusions & recommendations

- Multiple presentations, delay in diagnosis & ineffective isolation were common
  - If we miss opportunities to diagnose & isolate, our control guidelines are not useful
  - Need to continue improving awareness of measles among medical staff

Australian National University ncirs

## Conclusions & recommendations

- Individuals may be more infectious during rash stage
  - Focus on improving identification of measles rash during outbreaks
  - Raising level of suspicion of rashes during outbreaks

Australian National University ncirs

**Conclusions & recommendations**

- **The 2 hour contact tracing rule may not be appropriate during busy outbreaks**
  - Comprehensive review of the effectiveness of 2 hour rule beneficial
  - During times of limited resources it may be more effective to focus only on those who overlapped in time with source case

ncirs
NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

Australian National University ncirs ncirs

*Note: Data included in this presentation may differ from those included in the report in Part Two due to data having been updated.

# CHAPTER 5. DATA ANALYSIS

## Australian vaccine preventable disease epidemiological review: pertussis 2006–2012

# TABLE OF CONTENTS

# PREFACE

## Background and scope of the chapter

The National Centre for Immunisation Research and Surveillance (NCIRS) is contracted by the Department of Health (DOH) to deliver periodic vaccine preventable disease (VPD) reports. These reports utilise routinely collected surveillance data to analyse disease trends in the context of the current National Immunisation Program (NIP). I was asked to write the pertussis report covering the years 2006–2012; it is included in this chapter.

## Investigatory role

To conduct the pertussis analysis, I acquired the complete pertussis notifications dataset from the National Notifiable Disease Surveillance System (NNDSS). With instruction and oversight from Dr Helen Quinn, I performed all cleaning, recoding of variables, calculation of rates and incidence rate ratios, and table and graph generation. Dr Quinn extracted, cleaned and organised the hospitalisation and mortality data. For the report included within this chapter, co-authored by Dr Quinn and Professor Peter McIntyre, I drafted, revised, and conducted all analysis and data presentation with one exception: the graph displaying the ratio of hospitalisation to notification rates for those aged <6 months (Figure 5.6). This was created by Dr Quinn for a previous report.

## Lessons learned

The lessons learned from this project were substantial. With limited data analysis experience coming into the Master of Philosophy Applied Epidemiology (MAE) program, even cleaning a large dataset was a task I was unsure how to approach. However, my work placement supervisor Dr Quinn was extremely patient. After walking me through the basics of using Excel as a starting point to explore the data,

she worked closely with me to understand what was necessary to make the dataset workable for my purposes, including identifying and removing extraneous information, and re-coding and creating new variables, and generating a series of charts and graphs appropriate for my report.

Later, as a result of the MAE intensive course in data analysis, I became comfortable with Stata and its methodologies. Realising it was a superior tool for analysis, I used the program to re-do all my prior Excel calculations, although I was, nonetheless, still appreciative of having taken the time to learn Excel. As someone who was rather apprehensive about conducting data analysis and using statistical software, I surprised myself with my capabilities. More surprisingly, I realised I actually enjoyed data analysis; it was so different from working with words, my more familiar medium.

Beyond conquering my data analysis apprehensions, and having armed myself with skills in Excel and Stata, I learned several smaller, specific lessons. Firstly, I realised that working with such large datasets can be painstaking, and errors easily introduced. The 'results' generated in my Excel analysis did not initially match the numbers outputted when I employed Stata; this required a careful re-checking of my initial cleaning, categorisation/re-coding, etc. Secondly, this was my first exposure to NNDSS and Australian Bureau of Statistics (ABS) data and this required some familiarisation before being able to work with each dataset.

The analytical interpretation of the data was also instructive. Analysing trends in VPDs proved complex; for example, maintaining linkages between which age cohort received which vaccination in which year was challenging. This project also gave me a deeper appreciation for the complexities involved in formulating an effective vaccination policy. 'Targets' are in flux and dynamic, and issues of waning immunity and vaccine effectiveness must be factored in. Earlier, I might have predicted that data analysis would have been the only challenging component within this project; as it transpired, interpreting the results was equally taxing.

## Public health impact

As trends in VPDs are dynamic, periodically compiling surveillance data and analysing these trends is imperative. This input is vital to informing effective and appropriate immunisation policy. To that end, the report which follows was written in fulfilment of NCIRS's requirement to conduct VPD reports for the DOH. NCIRS's VPD reports are widely acknowledged by the Australian health community as comprehensive references for VPD trends.

In addition to being provided to the DOH, this report was also provided to the Communicable Diseases Network Australia (CDNA) and the Australian Technical Advisory Group on Immunisation (ATAGI) to advise stakeholders about the current epidemiology of pertussis. It will be published in *Communicable Diseases Intelligence* (CDI).

The results of this particular analysis (2006–2012) demonstrate that pertussis notification rates have remained at epidemic levels, with the very young being affected most severely. High rates among young children are suggestive of early waning of the acellular vaccine. This requires a review of the optimal age of vaccination, and whether or not booster doses—such as the 18 month old dose removed from the immunisation schedule in 2003—should be reconsidered. This report was submitted to the Pertussis Working Party. Components of it have been used in the Party's final advice recommending the re-instatement of the booster dose.

## Acknowledgements

I am indebted to Dr Quinn for the time spent teaching me how to approach and conduct data analysis for projects such as this, and also for her guidance on interpreting, presenting and writing up my results. The instruction I received in the MAE data analysis course was also crucial for improving my data analysis skill set. Lastly, Professor Peter McIntyre, co-author of the report, provided extremely valuable feedback and ideas regarding the direction and framing of the analysis and manuscript.

I would also like to acknowledge the Vaccine Preventable Diseases Surveillance Section, Health Emergency Management Branch, Office of Health Protection, Australian Government DOH for data from the NNDSS, and the Hospitals Unit, Australian Institute of Health and Welfare (AIHW) for data from the National Hospital Morbidity Database.

# ABBREVIATIONS

| | |
|---|---|
| **ABS** | Australian Bureau of Statistics |
| **ACT** | Australian Capital Territory |
| **AIHW** | Australian Institute of Health & Welfare |
| **ATAGI** | Australian Technical Advisory Group on Immunisation |
| **CDI** | *Communicable Diseases Intelligence* (Journal) |
| **CDNA** | Communicable Diseases Network Australia |
| **DOH** | Department of Health |
| **DTP** | Diphtheria-Tetanus-Pertussis (Vaccine) |
| **DTPa** | Diphtheria-Tetanus-Acellular Pertussis (Vaccine) |
| **dTpa** | Reduced antigen content Diphtheria-Tetanus-Acellular Pertussis (Vaccine) |
| **DTPw** | Diphtheria-Tetanus-Whole Cell Pertussis (Vaccine) |
| **ICD** | International Statistical Classification of Diseases & Related Health Problems |
| **IgG** | Immunoglobulin G |
| **MAE** | Master of Philosophy Applied Epidemiology |
| **NCIRS** | National Centre for Immunisation Research & Surveillance |
| **NIP** | National Immunisation Program |
| **NNDSS** | National Notifiable Disease Surveillance System |
| **NSW** | New South Wales |

| | |
|---|---|
| **PCR** | Polymerase Chain Reaction |
| **VPD** | Vaccine Preventable Disease |
| **WHO** | World Health Organization |

# LIST OF TABLES

# LIST OF FIGURES

# ABSTRACT

Despite pertussis vaccine being available since the 1940s and immunisation programs using combined diphtheria-tetanus-pertussis vaccine (DTP) being in place since the mid-1950s, pertussis has been the most commonly notified VPD in Australia over the past 20 years. Pertussis notification and hospitalisation data have been available at the national level since 1993, and provide different perspectives for understanding epidemiological trends. This report follows on from a previous review of Australian pertussis epidemiology from 1995–2005 and summarises routinely collected notification, hospitalisation and mortality data for 2006–2012. During this seven year period, the average annual notification rate was more than 2.8 times that of the previous decade though hospitalisation and mortality rates have remained comparable to rates experienced in the previous decade. There was a significant change in the pattern of age-specific notification rates, with the steepest increases seen among children less than 10 years, especially those 2–4 years and 6–9 years of age. South Australia experienced a peak in notifications among those aged 5–9 and 10–12 years prior to other states and territories. Likely reasons for the overall increase in notifications as well as the changes in age-specific patterns include increased diagnostic testing and more rapid waning of effectiveness post vaccination with acellular compared to whole cell vaccines, exacerbated by cessation of the 18 month dose in the NIP from 2003.

# AUSTRALIAN VACCINE PREVENTABLE DISEASE EPIDEMIOLOGICAL REVIEW SERIES: PERTUSSIS 2006–2012

**Ms Alexis Pillsbury**[1,2], Master of Philosophy (Applied Epidemiology) Scholar

Dr Helen Quinn[1,3], Research Fellow

Professor Peter McIntyre[1,3], Director

Affiliation(s)

1. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), The Children's Hospital at Westmead and the University of Sydney, New South Wales, Australia.
2. National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australia.
3. Discipline of Paediatrics and Child Health, University of Sydney, The Children's Hospital at Westmead, Westmead, New South Wales 2145, Australia.

**Manuscript submitted to *Communicable Diseases Intelligence* as part of an NCIRS series**

# INTRODUCTION

In Australia, universal childhood immunisation with combined DTP vaccine began in 1953 and was continued in the national schedule when it commenced in 1975. Since 1982, the primary schedule has recommended infant doses at 2, 4 and 6 months, but both the number and timing of booster doses and vaccines in use have changed substantially since then. Recent modifications have included the switch for all scheduled doses from the diphtheria-tetanus-whole cell pertussis vaccine (DTPw) to the diphtheria-tetanus-acellular pertussis vaccine (DTPa) in 1999; the change in recommendation for the 5th dose to be administered at 4 years rather than 4–5 years of age in 2000; the removal of the 18 month booster in 2003; and the addition in 2004 of the adolescent booster reduced antigen content diphtheria-tetanus-acellular pertussis vaccine dose (dTpa) recommended with varying ages of administration by jurisdiction.[1]

Despite a well-established immunisation program and high vaccine coverage,[2] pertussis continues to be the most commonly notified VPD in Australia,[3] with increases in national notification rates over the past 20 years, in different age groups and epidemic cycles. Similar trends have occurred in other developed countries, though typically later than Australia.[4-7]

Several changes in diagnostic testing are likely to have contributed to the observed increase in pertussis notifications. First, the availability and use of serologic testing in adolescents and adults increased from the early 1990s. Second, from 2000, polymerase chain reaction (PCR) became available as a diagnostic test, initially in hospitals and then, with changes in reimbursement arrangements, also in primary care from 2007.[8] Third, use in primary care was facilitated by laboratories accepting specimens collected by throat swab, as well as nasopharyngeal aspirate, which particularly facilitated testing of young children. Laboratories are legally mandated to report positive tests for pertussis under Australian public health laws. In the case of notifications based on PCR, which are accepted as confirmed cases without

supplementary clinical criteria being required, diagnostic testing changes directly contributed to the rise in notifications.

Beyond the influence of changes in diagnostic practice, recent evidence has shown that protection from the acellular vaccine—universally adopted in Australia in 1999—is not as long-lasting as that from the whole cell vaccine.[9-11] In turn, shorter duration of immunity has the potential to magnify the impact of changes to the vaccination schedule with subsequent epidemic cycles. This is likely to have occurred among children aged 1–3 years following the removal of the 18 month booster.[12]

This analysis provides a detailed overview of Australian pertussis trends nationally, regionally and by age group from 2006–2012, following a similar review for the period 1995–2005. Trends are considered both in historical context and in the context of recent changes to the NIP.

# METHODS

## Data sources

### *Notifications*

In Australia, pertussis is notifiable by each state and territory; both confirmed and probable pertussis cases require notification. For the period under review, a confirmed case required either laboratory confirmation or a combination of laboratory suggestive and clinical evidence. A confirmed case could also consist of clinical and epidemiological evidence. A probable case required clinical evidence only. Laboratory confirmation included isolation of *Bordetella pertussis* or detection by PCR. Laboratory suggestive evidence included serology (single point high titre or seroconversion) or an immunofluorescence assay.[13]

For this report, notification data were obtained from the NNDSS. All state and territory

pertussis notifications with a diagnosis date between 1 January 2006 and 31 December 2012 were included. Laboratory diagnostic data were available for all states and territories except Tasmania; limited data were available for South Australia. For all other jurisdictions, completeness ranged from 86.3% (Victoria) to 99.3% (Australian Capital Territory (ACT)). For the purpose of this review, where multiple diagnostic methods were recorded in the dataset, the case was classified as having been diagnosed by the most sensitive method.[14] Typically, this was PCR.

As part of this review, an ecological analysis of vaccine cohorts based on individual jurisdiction of birth was conducted. This analysis involved South Australia and New South Wales (NSW) as representing the two differing time periods when DTPa was adopted by states and territories. South Australia and the Northern Territory introduced the acellular vaccine in 1997; the other states and territories did so in 1999. For each of these two jurisdictions, further sub-grouping was performed based on birth cohort and subsequent eligibility for different vaccine types: whole cell vaccine for all doses, whole cell vaccine for the primary series, or acellular vaccine for all doses. Rates over time for children aged 5–9 and 10–12 years were then calculated for these groups.

This report forms an extension of a previous analysis which reviewed pertussis trends from 1995–2005. Data from the previous analysis have been referred to and incorporated into several graphs in order to provide broader context.[3]

### *Hospitalisation and mortality data*

Hospitalisation data were obtained from the AIHW National Hospital Morbidity Database which compiles administrative, demographic and clinical information about patients admitted to public and private hospitals. For this report, all hospitalisation admissions between 1 January 2006 and 31 December 2010 were included. Eligible hospitalisation admissions were extracted based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM), code A37 (whooping cough), or a subcode, listed as the

principal or other diagnosis.

Mortality data were obtained from the NNDSS data field which recorded whether the notified case had died from pertussis.

### *Population estimates*

National, jurisdictional and age-specific mid-year estimated resident population data were obtained from the ABS.[15]

## Data analysis

Annual notification numbers and diagnostic test data were reviewed nationally, regionally, and by age group for the time period of 2006–2012. National, regional and age group-specific rates were calculated using ABS population data. Similarly, hospitalisations were reviewed for 2006–2010 with national, regional and age group-specific rates calculated. Medians were used to summarise hospitalisation admission length of stay data. Mortality data were reviewed nationally by age group for the period of 2006–2012.

Analysis was conducted using Stata 12 and Excel 2010.

# RESULTS

## Secular trends

From 2006–2012, 156,200 notifications were recorded by the NNDSS (Table 5.1). The average annual national rate for this seven year period was 103.1 per 100,000 population, varying from a low of 23.1 to a high of 173.3 per 100,000 population in 2007 and 2011 respectively. Though national notification rates initially fell during the period 2006–2007 from those in 2005, rates steadily increased from 2008 through 2011. This pattern of decreasing notifications followed by a consistently upward trend with varying peak years was largely repeated across all jurisdictions but in different time frames. In 2006 and 2007, notification rates for those <15 years of age were lower than those aged ≥15 years, but this pattern reversed in 2008–2012 such that notification rates in those <15 years of age became more than double those in persons ≥15 years (Figure 5.1).

**Table 5.1. Annual pertussis notification and hospitalisation rates per 100,000 population, Australia, by state and territory, 2006–2012***

| Year | | State or territory | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | SA | NSW | ACT | Qld | Tas | WA | NT | Vic | Aus |
| 2006 | Notifications | 139.0 | 54.0 | 77.2 | 53.1 | 8.4 | 12.9 | 46.1 | 20.8 | 47.2 |
| | Hospitalisations | 4.9 | 3.2 | 0.3 | 2.6 | 0.4 | 0.8 | 4.3 | 1.0 | 2.3 |
| 2007 | Notifications | 23.9 | 23.5 | 28.4 | 36.7 | 5.1 | 6.3 | 12.6 | 20.2 | 23.1 |
| | Hospitalisations | 1.4 | 1.5 | 0.6 | 2.1 | 0.2 | 0.3 | 1.4 | 1.2 | 1.3 |
| 2008 | Notifications | 92.5 | 108.0 | 41.7 | 53.0 | 39.9 | 21.3 | **216.4** | 32.7 | 66.8 |
| | Hospitalisations | 3.9 | 5.6 | 2.0 | 2.7 | 2.2 | 1.9 | 14.0 | 2.0 | 3.6 |
| 2009 | Notifications | 332.6 | 176.1 | 99.2 | 142.4 | 122.8 | 34.7 | 94.8 | 70.3 | 136.8 |
| | Hospitalisations | 14.2 | 9.4 | 4.0 | 6.9 | 5.8 | 2.4 | 7.9 | 3.8 | 7.0 |
| 2010 | Notifications | **453.6** | 130.4 | 197.6 | 185.8 | 55.3 | 63.2 | 142.8 | 129.5 | 157.7 |
| | Hospitalisations | 17.4 | 4.6 | 3.0 | 6.8 | 2.8 | 3.3 | 10.4 | 6.0 | 6.2 |
| 2011 | Notifications | 143.4 | **182.3** | **225.4** | **200.9** | 68.9 | **169.6** | 163.4 | **156.3** | **173.3** |
| | Hospitalisations | | | | | | | | | |
| 2012 | Notifications | 54.4 | 80.7 | 117.7 | 168.3 | **246.5** | 142.8 | 128.0 | 79.8 | 107.6 |
| Total number notifications | | 20039 | 53573 | 2826 | 36926 | 2777 | 10444 | 1820 | 27795 | 156200 |
| Total number hospitalisations | | 676 | 1700 | 35 | 911 | 57 | 194 | 85 | 750 | 4408 |
| Average rate notifications | | 177.8 | 108.6 | 114.3 | 122.0 | 79.0 | 67.0 | 116.2 | 74.0 | 103.1 |
| Average rate hospitalisations | | 8.5 | 4.9 | 2.0 | 4.3 | 2.3 | 1.8 | 7.7 | 2.8 | 4.1 |

*Note: Hospitalisation data available through 2010.

Figures in bold are peak notification rates for each state/territory, 2006–2012.

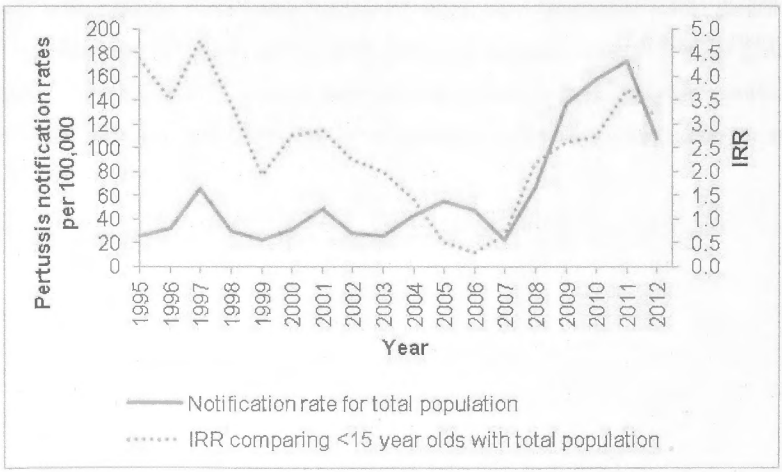



**Figure 5.1. Pertussis notification rates per 100,000 population by year of onset, and incidence rate ratios (IRRs) comparing <15 year olds with the remainder of the population, Australia, 1995–2012**

ICD coded hospitalisations are collected by a separate process to notifications, with hospitalisation status not available in the NNDSS data set. Between 2006–2010, 4,408 hospitalisations were coded as pertussis comprising only 3.9–5.6% of the number of notifications over this period; the pattern of hospitalisation rates generally reflected those of notification rates (Table 5.1).

Over this period, 73.8% of total ICD coded hospitalisations had a whooping cough code as the principal diagnosis, decreasing with age from 89.2% for those aged <6 months, to 50.0% for those aged ≥65 years. Between 2006–2010, there was little difference between the average percentage of all age primary diagnoses coded as *Bordetella pertussis* (49.0%) compared with those coded as whooping cough unspecified. However, for those aged <6 months, the percentage of diagnoses coded as *Bordetella pertussis* (57.6%) increased, becoming in 2010 higher than the proportion coded as whooping cough unspecified for the first time in the five year period since 2006.

## State and territory variations

Jurisdictional notification rates for the period of 2006–2012 are presented in Table 5.1.

Together, NSW (n=53,573) and Queensland (n=36,926) contributed 57.9% of all national notifications during the seven year period. South Australia had the highest annual notification rate at 453.6 per 100,000 (2010) as well as the highest average jurisdictional rate for the seven year period at 177.8 per 100,000. All states and territories, however, reported peak average annual notification rates which ranged from 1.8 to 4.6 times higher than those for the same jurisdictions during the previous decade.[3] With respect to timing, the Northern Territory and Tasmania had earlier epidemic peaks occurring in 2008–2009; most other states and territories peaked later between 2010–2011, with Western Australia the last to reach epidemic levels in 2011–2012 (Table 5.1; Figure 5.2; Figure 5.3). By 2012, notification rates had decreased in most jurisdictions, with the notable exception of Tasmania where rates had climbed. Figure 5.2 and Figure 5.3 present notification patterns for each state and territory

during 2006–2012. Figure 5.3 also shows jurisdictional hospitalisation rates from 2006–2010, demonstrating that hospitalisation patterns closely followed notification patterns, but on a reduced scale.

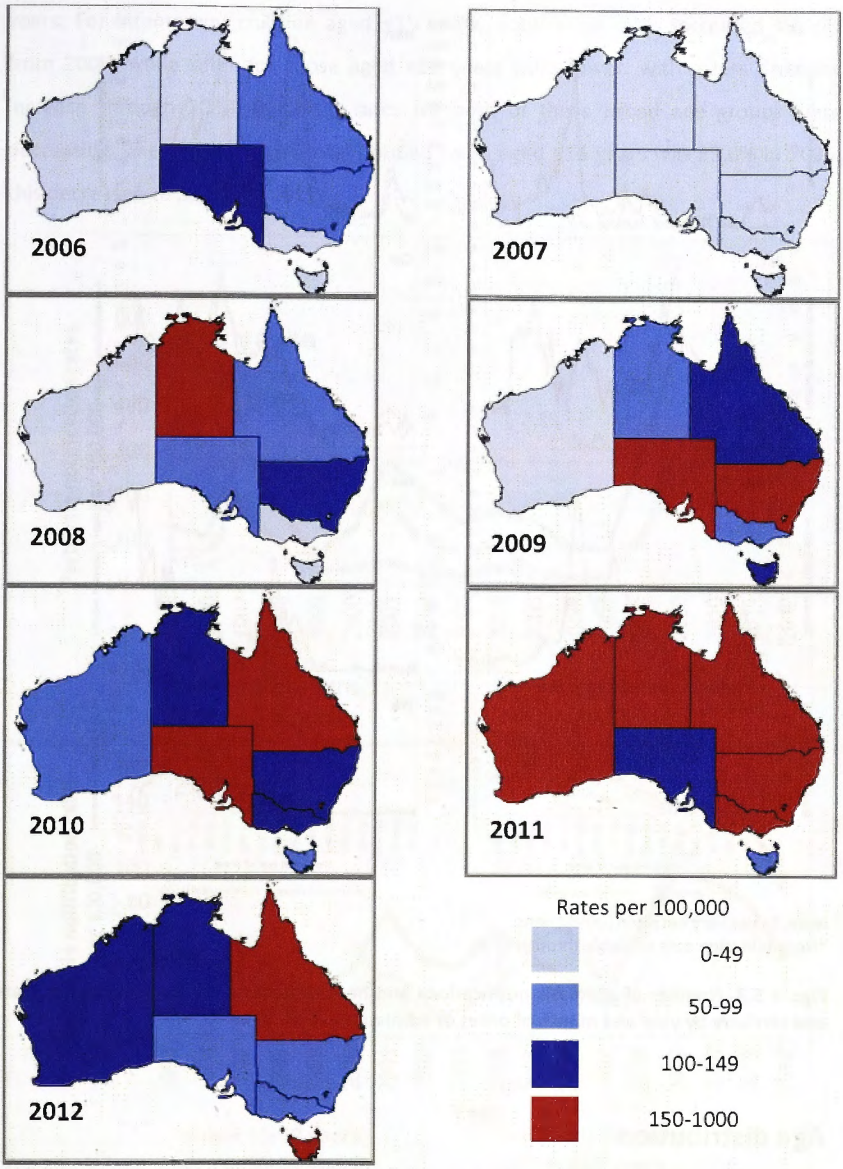
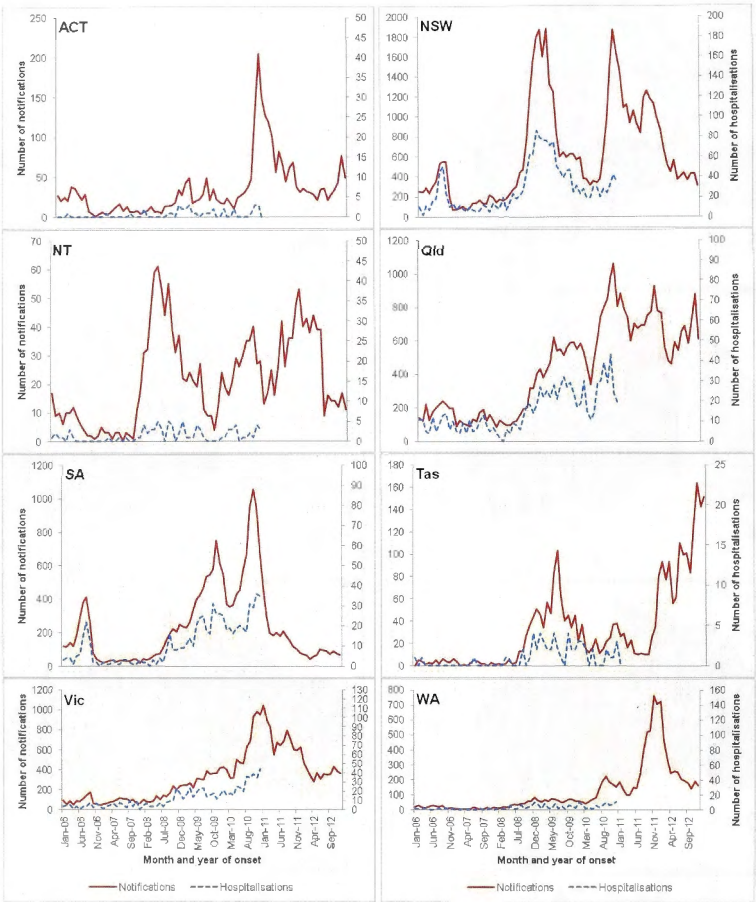



**Figure 5.2. Australian state and territory pertussis notification rates per 100,000 population by year, 2006–2012**



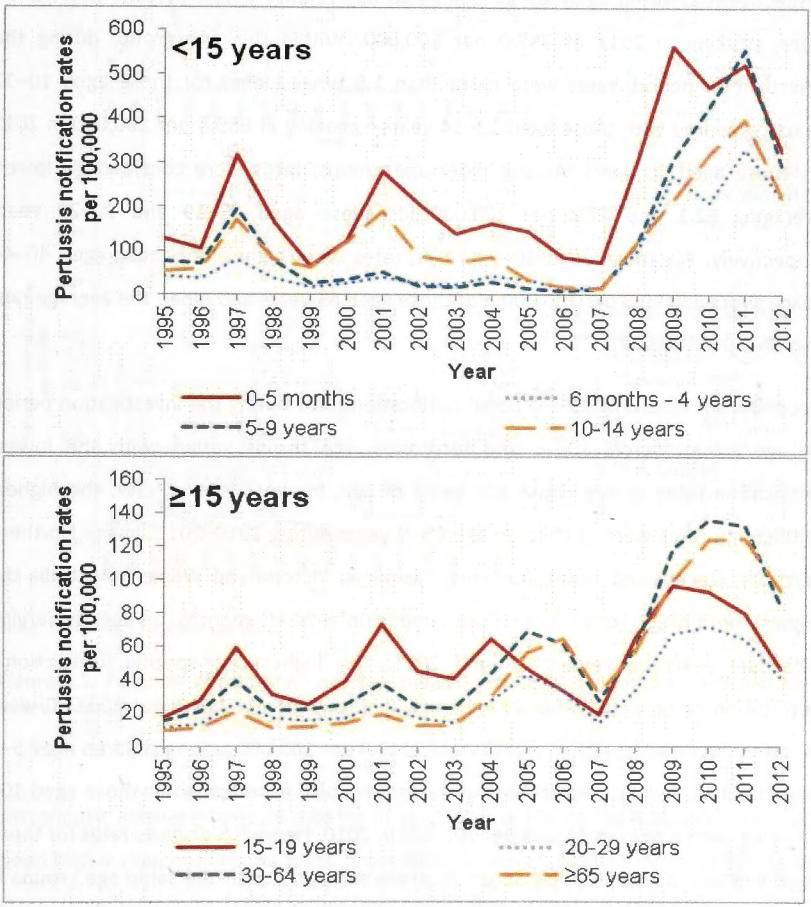

Note: Scales vary between jurisdictions.
*Hospitalisation data available through 2010.

**Figure 5.3. Number of pertussis notifications and hospitalisations for each Australian state and territory by year and month of onset or admission, 2006–2012***

## Age distribution

Age-specific notification rates are displayed in Figure 5.4. During the seven year period, the average notification rate for those aged <15 years was 205.6 per 100,000 (range: 16.4–434.3) compared with 79.0 per 100,000 (range: 24.8–118.5) for those aged ≥15

years. For infants and children aged <15 years, notification rates increased steeply from 2007, while rates for those aged ≥15 years were lower, with a less dramatic increase through 2010. By 2012, rates for both of these broad age groups were decreasing. The proportion of total notified cases aged ≥15 years was 93.0% in 2006; this decreased to 57.8% by 2012.

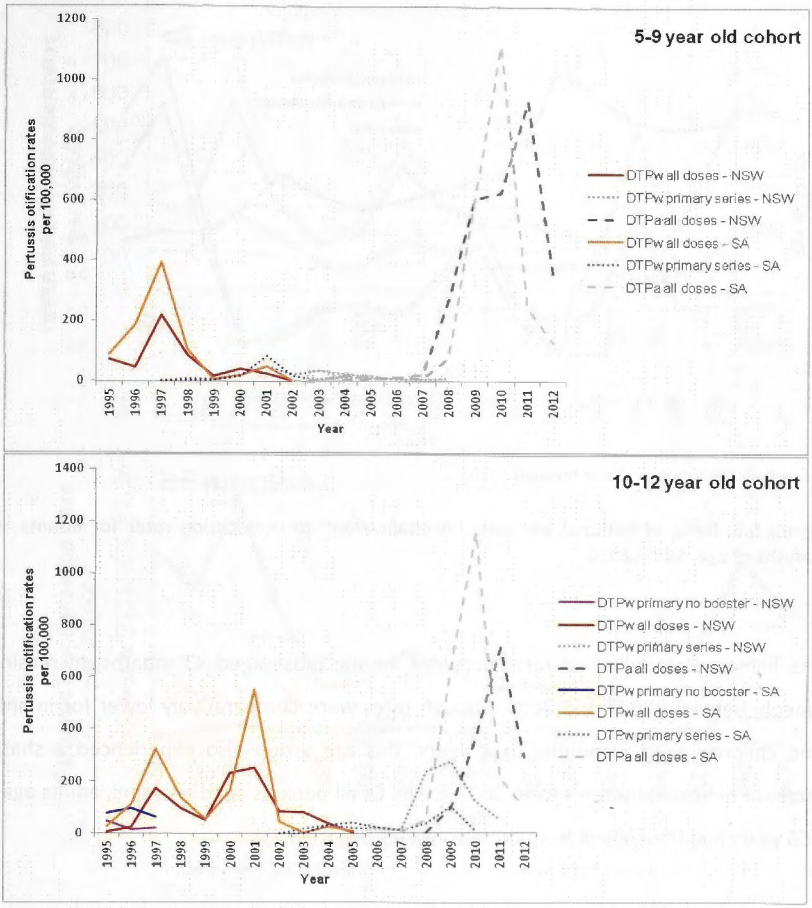



Note: Scales vary between panels.

**Figure 5.4. Age-specific pertussis notification rates per 100,000 population for groups <15 and ≥15 years of age, Australia, 1995–2012**

From 2008–2011, high notification rates were seen in infants aged 0–5 months (Figure 5.4). The highest rates for those aged 6 months–4 years were seen in children aged 3 years, peaking at 411.0 per 100,000 in 2011. However, the highest rates among all age groups were those for children aged 5–9 years. From 2008, rates among children in this age group were incrementally higher for each single year age group from 5–8 years, peaking at 627.9 and 651.0 per 100,000 for those aged 7 and 8 years respectively. Children aged 10–14 years also had relatively high average notification rates, peaking in 2011 at 397.0 per 100,000. Within this age group, during the investigation period, rates were more than 1.8 times higher for those aged 10–12 years compared with those aged 13–14 years—peaking at 659.5 per 100,000 in 2011 for those aged 10 years. Among older age groups, rates were considerably lower, averaging 62.1 and 47.2 per 100,000 for those aged 15–19 and 20–29 years respectively. For those aged 30–64 years, rates were highest for those aged 40–44 years, averaging 99.8 per 100,000. For those aged 65 years and older, the average rate was 86.0 per 100,000.

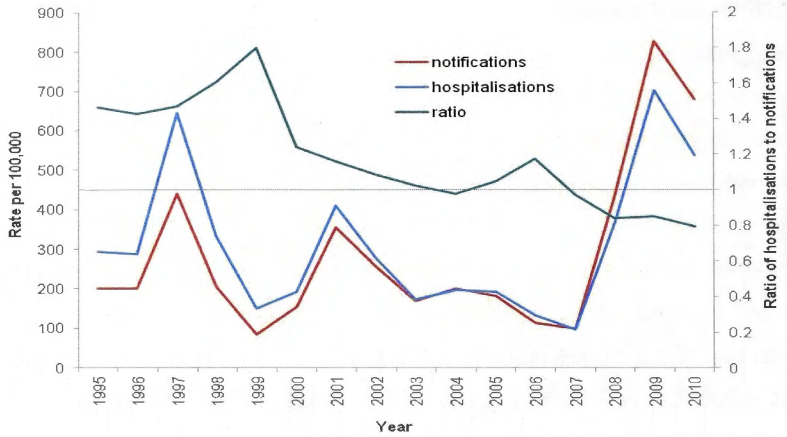
Appendix 5.A details all jurisdictional notification rates during the investigation period by age group. Across states and territories, age trends varied, with the lowest notification rates among those ≥15 years of age. In the ACT and NSW, the highest notification rates were in children aged 5–9 years during 2010–2011. In the Northern Territory, Queensland, South Australia, Tasmania, Victoria and Western Australia the highest notification rates were seen among infants <6 months of age in varying individual years between 2008 and 2011. The highest age-specific jurisdictional notification rates were in South Australia, where rates of 1119.3 per 100,000 were recorded for infants aged <6 months and 1117.4 per 100,000 among children aged 5–9 years in 2010. In South Australia, high rates were also experienced by those aged 10–12 years, with a peak of 1158.9 per 100,000 in 2010. Figure 5.5 displays rates for those aged 5–9 and 10–12 years for South Australia compared with the same age groups in NSW by birth cohort. Rates peaked for those aged 5–9 and 10–12 years in South Australia a year earlier than in NSW.




Note: Scales vary between panels.

**Figure 5.5. Pertussis notification rates per 100,000 population for children 5–9 and 10–12 years of age, by birth cohort, NSW and South Australia, 1995–2012**

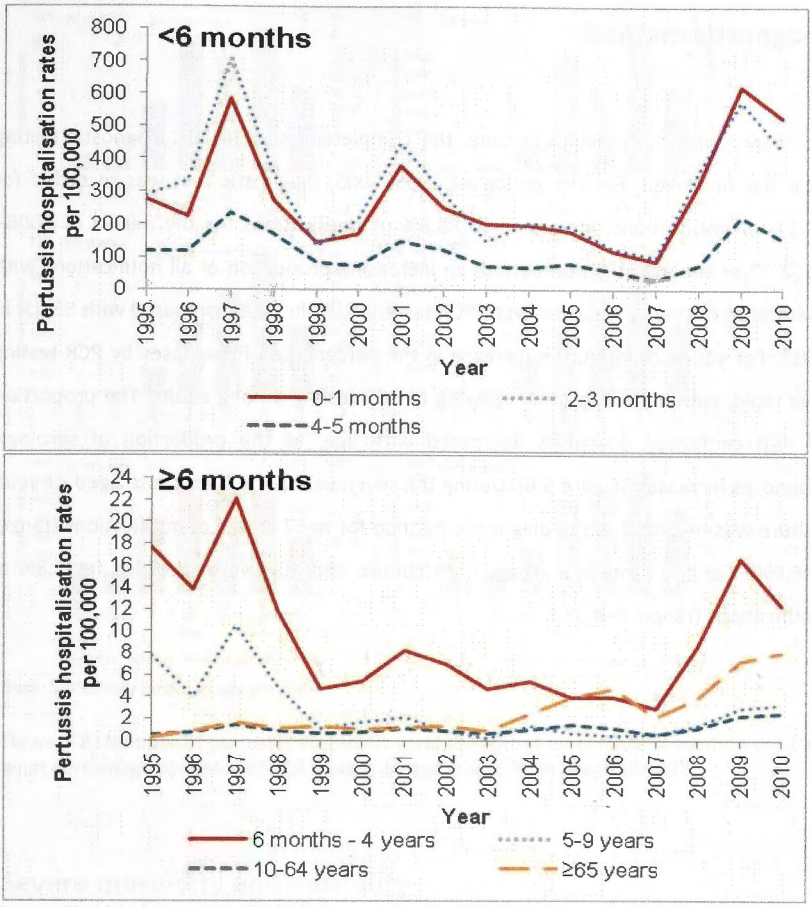
Historically, among infants <6 months of age, rates of ICD coded hospitalisations have been higher than notification rates. From 2007, however, notification rates for this age group have been consistently higher than hospitalisation rates (Figure 5.6).




*Hospitalisation data available through 2010.

**Figure 5.6. Ratio of national pertussis hospitalisation* to notification rates for infants <6 months of age, 1995–2010**

The highest hospitalisation rates occurred among those aged ≤3 months, increasing steeply between 2007 and 2009. Though rates were comparatively lower for infants and children aged 6 months to 4 years, this age group also experienced a sharp increase in hospitalisations from 2007–2009. Of all persons aged >4 years, adults aged ≥65 years had the highest hospitalisation rates (Figure 5.7).

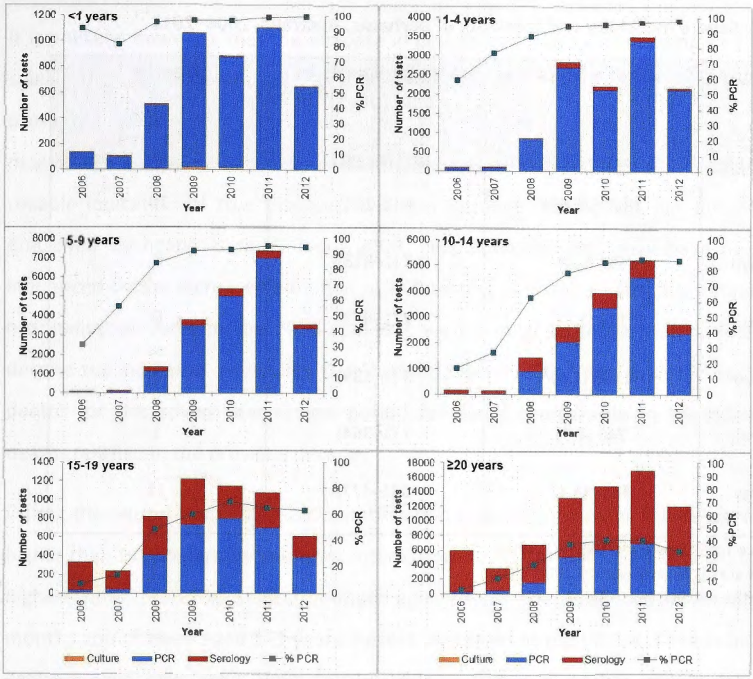



Note: Scales vary between panels.
*Hospitalisation data available through 2010.

**Figure 5.7. Age-specific pertussis hospitalisation rates per 100,000 population for groups <6 months and ≥6 months of age, Australia, 1995–2010***

## Diagnostic method

Compared with the previous decade, the completeness of NNDSS diagnostic testing data has improved. For the period of 1995–2005, diagnostic test was recorded for 50.1% of notifications, increasing to 85.8% of notifications for the period of 2006–2012. Over the investigation period, an increasing proportion of all notifications with method of diagnosis recorded were PCR tested: 6.9% in 2006 compared with 58.7% in 2012. For young children, the increase in the percentage of diagnoses by PCR testing was rapid, with a more gradual upswing of PCR testing among adults. The proportion of PCR confirmed diagnoses decreased with age, as the proportion of serologic diagnoses increased (Figure 5.8). During the seven year period, for those aged <1 year, culture was recorded as the diagnostic method for n=67 (1.5%) of notifications (range: 0–6.0%). For the same age group, both culture and PCR were recorded for 1.8% of notifications (range: 0–4.3%).




Note: Scales vary between age groups.

**Figure 5.8. Number of pertussis diagnostic tests conducted by diagnostic method used and what percentage consisted of PCR testing, by age group, Australia, 2006–2012**

## Severe morbidity and mortality

During the period of investigation, 11 notified cases were reported to have died from pertussis. Of these, ten deaths were in unvaccinated infants <2 months of age and one was an adult aged 70 years. Though there were twice as many infants <6 months of age hospitalised for pertussis than adults aged ≥65 years, the median length of stay per hospital admission was longer for the older adult age group (median: 7 days) than for the infant group (median: 4 days; Table 5.2).

Table 5.2. Severe morbidity and mortality of pertussis, Australia, 2006–2012[*,†]

| Age group | Hospital admissions | Median length of stay (days)[†] | Deaths[*] |
|---|---|---|---|
| | n (rate per 100,000) | n (range) | n |
| <6mo[‡] | 1832 (257.9) | 4 (1–292) | 10 |
| 6mo-4yo | 557 (9.0) | 2 (1–313) | 0 |
| 5-9yo | 113 (1.7) | 2 (1–477) | 0 |
| 10-64yo | 1166 (1.4) | 3 (1–139) | 0 |
| ≥65yo | 740 (4.9) | 7 (1–364) | 1 |
| All ages | 4408 (4.1) | 3 (1–477) | 11 |

[*]Deaths are for the period 2006–2012.
[†]Length of stay is for the period 2006–2010.
[‡]Mo: months old; yo: years old

# DISCUSSION

Between 2006–2012, the average notification rate (103.1 per 100,000) was 2.8 times that of the previous decade.[3] Unlike the previous decade, the expected 3–4 year epidemic cycles[16] were not apparent, replaced by sustained epidemic level rates, which peaked in 2009 and 2011 depending upon jurisdiction. This national picture is similar to previously published jurisdictional reviews of notifications for the same time period.[17, 18]

Although notifications are still believed to be underreported,[19, 20] improved surveillance and laboratory diagnostics as well as heightened awareness among clinicians have led to increased testing and notification of disease.[21-23] In particular, the general availability of commercial PCR kits[24] as well as the high sensitivity of PCR testing—as has been noted elsewhere[25]—have encouraged clinicians to test more, thus contributing to the rise in notifications.

It is unlikely, however, that the increase in pertussis notifications documented here is solely attributable to increased testing and diagnosis.[8, 12, 25] The hospitalisation rates presented in this report—which rose similarly to notification rates but not to the same magnitude—support this claim, as hospitalisation data are likely a more stable and reliable indication of true disease incidence. Because PCR testing has been widely employed by hospitals since about 2000, hospitalisation data may have been less influenced by the increased adoption of PCR testing in primary care. It is notable that hospitalisation rates in the 2009 epidemic were similar to those recorded in 1997, despite the increased availability of PCR testing from 2000.[26] Similarly, the number of deaths for this seven year review period remained comparable to the number of deaths notified in the previous decade.

During the period from 1995–2005, notification rates for Australian adults were much higher than in comparable countries internationally.[27-29] In contrast, in 2006–2012 the highest rates occurred among younger age groups, specifically in infants aged <6 months and children aged 5–9 years. Recent outbreaks in the US, UK, Canada and New Zealand have also been characterised by high rates in infants too young to be vaccinated.[4, 30-33] High rates in infants have been common for several decades. When notifications were largely reliant upon clinical diagnoses, higher rates were often detected in hospitalisation data because infant cases admitted to hospital were not notified. Since the increased use of PCR testing in Australia, however, this differential between notification and hospitalisation data for infants has diminished.[34]

Although evidence that a single dose of DTPa provides some level of protection against severe disease, infants are still vulnerable to infection prior to receiving the first scheduled dose, which is evident by the fact that 10 of 11 deaths reported in this seven year period were in infants aged <2 months.[35, 36] Recent trials have investigated the delivery of pertussis vaccine at birth.[37-40] The cocooning strategy (vaccinating close contacts of infants to reduce the likelihood of exposure) and maternal vaccination have been recommended for preventing infection in very young infants and have been given equal preference in the most recent Australian Immunisation Handbook.[41] Maternal vaccination has also been recommended by the US, UK, Canada and New

Zealand.[30, 31, 42, 43]

High rates in children may have resulted in part from the NIP switch to the DTPa vaccine which does not confer immunity for as long as the DTPw vaccine.[10, 44-49] Specific estimates of the duration of immunity afforded by the whole-cell vaccine range from 4–14 years, though studies suggest that immunity conferred by the acellular vaccine may only last five years or less.[9, 50] Average notification rates from 2006–2012 for children aged 7 and 8 years were more than four times as high as those experienced by the same age group from 1995–2005. This suggests that immunity waned in the period following receipt of the 4 year old dose, for which coverage was estimated to be high, [51-53] before the adolescent booster could be administered. Similarly, high rates among US children aged 8–12 years were documented from 2005 and correspond to the first cohort of children to receive a schedule containing all acellular vaccines.[54, 55] In Australia, at the state and territory level, the DTPa vaccine was adopted for the primary series in South Australia and the Northern Territory in 1997 before being adopted Australia-wide for all childhood doses in 1999. This is likely to have contributed to notification rates for those aged 5–9 and 10–12 years in South Australia peaking earlier than in NSW, despite these states sharing similar overall epidemic patterns.

NIP schedule changes, specifically the 2003 removal of the 18 month booster dose, likely also influenced notification rates among younger age groups by exacerbating the impact of the decreased efficacy and longevity of the acellular vaccine. The removal of the 18 month booster expanded the time interval between doses from 6 months to 4 years of age leaving those aged 1–3 years vulnerable to waning immunity and resulting in record high notification rates for those aged 1–4 years from 2008.[12] Australian serosurvey results from 2007 support this claim, reporting that among children 1–4 years of age, prevalence of undetectable immunoglobulin G (IgG) levels had increased from 25% in 1997–98 to 62% in 2007.[12]

Based on evidence of waning immunity, as well as evidence that toddlers serve as an important source of infection for infants too young to be vaccinated,[56-58] the current Immunisation Handbook advises that an additional dose of DTPa in the 2nd year of life

will minimise the likelihood of a child developing pertussis prior to their scheduled booster dose at 3.5 to 4 years of age.[41] This is in line with the World Health Organization's (WHO's) 2010 recommendation that a booster be given in the second year of life unless country-specific epidemiological evidence supports delaying this until preschool.[59]

The decreased notification rates among older age groups demonstrated in this analysis were likely partially influenced by the 2003 NIP addition of the adolescent booster recommended for those aged 15–17 years. The reduced antigen booster (dTpa) employed for the adolescent dose has been demonstrated effective, despite variation in coverage and timing of programs across state and territories.[60, 61] Both the US and Canada have reported temporally similar decreases in disease among adolescents following the addition of adolescent boosters.[62, 63] In response to concern about waning immunity, ATAGI has recommended shifting the fifth dose to 11–13 years to decrease the time between the primary childhood series and adolescent booster.[64]

Though notification rates appeared to decrease somewhat in 2012, average rates for the period of investigation were dramatically higher than those experienced in the previous decade. Interpretations of these high rates, however, must be kept within the proper context. Because of the increase in community PCR testing, baseline pertussis rates may well remain higher than they were prior to this change in diagnostic practice. Nevertheless, in light of the fact that this review demonstrates that pertussis notification rates are once again highest among the young, strategies targeted at reducing disease among infants must continue to be pursued. Due to the dynamic nature of pertussis immunity, it is imperative to continue exploring a broad range of both scientific and policy solutions.

# REFERENCES


1. National Centre for Immunisation Research and Surveillance (NCIRS). Significant events in diptheria, tetanus and pertussis vaccination practice in Australia. 2012 [cited 2012 October 21]; Available from: http://www.ncirs.edu.au/immunisation/history/Diphtheria-tetanus-pertussis-history-July-2012.pdf.

2. Australian Government Department of Human Services. Australian Childhood Immunisation Register (ACIR) statistics. 2012 [cited 2012 October 20]; Available from: http://www.medicareaustralia.gov.au/provider/patients/acir/statistics.jsp#N1002D.

3. Quinn HE, McIntyre, P. Pertussis epidemiology in Australia over the decade 1995-2005 - trends by region and age group. Communicable Diseases Intelligence. 2007;31(2):205-15.

4. Cherry J. Epidemic pertussis in 2012 - the resurgence of a vaccine-preventable disease. N Engl J Med. 2012;367:785-7.

5. Wirsing von König C, Riffelman M. Pertussis: an old disease in new clothes. Eurosurveillance. 2007;12(9).

6. Winter K, Harriman K, Zipprich J, Schechter R, Talarico J, Watt J, et al. California pertussis epidemic, 2010. The Journal of Pediatrics. 2012:1-6.

7. Centers for Disease Control and Prevention (CDC). Pertussis epidemic - Washington, 2012. MMWR. 2012;61(28):517-22.

8. Kaczmarek M, Valenti L, Kelly H, Ware R, Britt H, Lambert S. Seven-fold rise in likelihood of pertussis test requests in a stable set of Australian general practice encounters, 2000-2011. Med J Aust. 2013;198:624-8.

9. Wendelboe AM, Van Rie A, Salmaso S, JA E. Duration of immunity against pertussis after natural infection or vaccination. Pediatr Infect Dis J. 2005;24(5 Suppl):S58-S61.

10. Witt M, Arias L, Katz P, Truong E, D W. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to receipients of acellular pertussis vaccines in a large US cohort. Clin Infect Dis. 2013;56(9):1248-54.

11. Witt MA, Katz PH, Witt DJ. Unexpectedly Limited Durability of Immunity Following Acellular Pertussis Vaccination in Pre-Adolescents in a North American Outbreak. Clinical Infectious Diseases. 2012 March 15, 2012.

12. Campbell P, McIntyre P, Quinn H, Hueston L, Gilbert G, McVernon J. Increased population prevalence of low pertussis toxin antibody levels in young children

preceding a record pertussis epidemic in Australia. PLoS ONE. 2012;7(4):1-7.

13. Australian Government Department of Health and Ageing. Australian national notifiable diseases case definitions: pertussis case definition. 2004 [cited 2012 October 20]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-casedefs-cd_pertus.htm.

14. Australian Government Department of Health and Ageing. Australian national notifiable diseases case definitions. 2011 [cited 2012 October 24]; Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/cdna-casedefinitions.htm.

15. Australian Bureau of Statistics. Australian demographic statistics. 2012 [cited 2013 4 June 2012]; Available from: http://www.abs.gov.au/ausstats/abs@.nsf/mf/3101.0.

16. Wood N, Quinn HE, McIntyre P, Elliott E. Pertussis in infants: Preventing deaths and hospitalisations in the very young. Journal of Paediatrics and Child Health. 2008;44(4):161-5.

17. Spokes P, Quinn H, McAnulty J. Review of the 2008–2009 pertussis epidemic in NSW: notifications and hospitalisations. NSW Public Health Bulletin. 2010;21(7-8):167-73.

18. Clarke M, Rasiah K, Copland J, Watson M, Koehler A, Dowling K, et al. The pertussis epidemic: informing strategies for prevention of severe disease. Epidemiol Infect. 2012;17:1-9.

19. Allen C, Ferson M. Notification of infectious diseases by general practitioners: a quantitative and qualitative study. MJA. 2000;172(7):325-8.

20. Cherry JD. The epidemiology of pertussis: a comparison of the epidemiology of the disease pertussis with the epidemiology of Bordetella pertussis infection. Pediatrics. 2005;115(5):1422-7.

21. McIntyre P, Wood N. Pertussis in early infancy: disease burden and preventive strategies. Current Opinion in Infectious Diseases. 2009;22(3):215-23.

22. Bamberger ES, Srugo I. What is new in pertussis? Eur J Pediatr. 2008;167:133-9.

23. Cherry JD. The present and future control of pertussis. Clin Infect Dis. 2010;51:663-7.

24. McIntyre PB, Sintchenko V. The "how" of PCR testing for *Bordetella pertussis* depends on the "why". Clinical Infectious Diseases. 2012.

25. Fisman D, Tang P, Hauck T, Richardson S, Drews S, Low D, et al. Pertussis resurgence in Toronto, Canada: a population-based study including test-incidence feedback modeling. BMC Public Health. 2011;11:694.

26. Chiu C, Dey A, Wang H, Menzies R, Deeks S, Majahan D, et al. Vaccine preventable diseases in Australia, 2005 to 2007. Commun Dis Intell. 2010;34(Suppl):S1-S167.

27. Centers for Disease Control and Prevention (CDC). Pertussis (whooping cough) surveillance and reporting. [Internet] 2013 [cited 2013 December 3]; Available from: http://www.cdc.gov/pertussis/surv-reporting.html.

28. McIntyre P. Is Australia the world capital of pertussis? National pertussis workshop: strategies to prevent severe pertussis in the next decade; 25-26 August 2011; Sydney, Australia, 2011.

29. Kanitz E. Pertussis in Europe from 1980-2010- incidence and vaccination coverage. European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE); 6-8 November 2011; Stockholm, Sweden, 2011.

30. Public Health England. Pertussis (whooping cough) immunisation for pregnant women. [Internet] 2013 [cited 2013 November 23]; Available from: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/WhoopingCough/ImmunisationForPregnantWomen/http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/WhoopingCough/ImmunisationForPregnantWomen/.

31. Auckland Regional Public Health Service. Information about whooping cough (pertussis) immunisation during pregnancy. [Internet] 2013 [cited 2013 November 23]; Available from: http://www.arphs.govt.nz/Portals/0/Health%20Information/Communicable%20Disease/Pertussis/Pertussis%20Fact%20sheet%20Jan%202013/Whooping%20cough%20immunisation%20in%20pregrnancy%20January%202013.pdf.

32. Chiappini E, Stival A, Galli L, de Martino M. Pertussis re-emergence in the post-vaccination era. BMC Infectious Diseases. 2013;13(151):1-12.

33. Alphonso C. Whooping cough makes deadly return across Canada. The Globe and Mail. 2012 July 23.

34. Torvaldsen S, McIntyre P. Do variations in pertussis notifications reflect incidence or surveillance practices? A comparison of infant notification rates and hospitalisation data in NSW. NSW Public Health Bulletin. 2003;14(5):81-4.

35. Hviid A, Stellfeld M, Andersen PH, Wohlfahrt J, Melbye M. Impact of routine vaccination with a pertussis toxoid vaccine in Denmark. Vaccine. 2004;22:3530-4.

36. Quinn H, Snelling T, Macartney K, McIntyre P. Duration of protection after first dose of acellular pertussis vaccine in infants. Pediatrics. 2014;Epub (10 February).

37. Belloni C, De Silvestri A, Tinelli C, Avanzini MA, Marconi M, Strano F, et al. Immunogenicity of a three-component acellular pertussis vaccine administered at birth.

Pediatrics. 2003;111(5 Pt 1):1042-5.
38. Halasa NB, O'Shea A, Shi JR, Lafleur BJ, Edwards KM. Poor immune responses to a birth dose of diptheria, tetanus, and acellular pertussis vaccine. J Pediatr. 2008;153(3):327-32.
39. Knuf M, Schmitt HJ, Wolter J, Schuerman L, Jacquet JM, Kieninger D, et al. Neonatal vaccination with an acellular pertussis vaccine accelerates the acquisition of pertussis antibodies in infants. J Pediatr. 2008;152(5):655-60.
40. Wood N, McIntyre P, Marshall H, Roberton D. Acellular Pertussis Vaccine at Birth and One Month Induces Antibody Responses By Two Months of Age. Pediatric Infectious Disease J. 2010;29(3):209-15.
41. Australian Technical Advisory Group on Immunisation (ATAGI). The Australian Immunisation Handbook. 10th ed. Canberra: Australian Government Department of Health and Ageing; 2013.
42. Matlow J, Pupco A, Bozzo P, Koren G. Tdap vaccination during pregnancy to reduce pertussis infection in young infants. Canadian Family Physician. 2013;59(5):497-8.
43. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months --- Advisory Committee on Immunization Practices (ACIP), 2011. MMWR 2011.
44. Stehr K, Cherry JD, Heininger U, Schmitt-Grohé S, Uberall M, Laussucq S, et al. A comparative efficacy trial in Germany in infants who received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP vaccine, or DT vaccine. Pediatrics. 1998;101:1-11.
45. Schmitt HJ, von König CH, Neiss A, Bogaerts H, Bock HL, Schulte-Wissermann H, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA. 1996;275:37-41.
46. Liese JG, Meschievitz CK, Harzer E, Froeschle J, Hosbach P, Hoppe JE, et al. Efficacy of a two-component acellular pertussis vaccine in infants. Pediatr Infect Dis J. 1997;16:1038-44.
47. Simondon F, Preziosi MP, Yam A, Kane CT, Chabirand L, Iteman I, et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine. 1997;15:1606-12.
48. Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H, Ad Hoc Group for the Study of Pertussis Vaccines. Randomised controlled trial of two-component, three-

component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Lancet. 1997;350:1569-77.

49. Sheridan SL, Ware RS, Grimwood K, Lambert SB. Number and order of whole cell pertussis vaccines in infancy and disease protection. JAMA. 2012;308(5):454-6.

50. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med. 2012;367:1012-9.

51. Hull B, Deeks S, Menzies R, McIntyre P. Immunisation coverage annual report 2007. Commun Dis Intell. 2009;33:170-87.

52. Hull B, Mahajan D, Dey A, Menzies R, McIntyre P. Immunisation coverage annual report 2008. Commun Dis Intell. 2010;34(3):241-58.

53. Hull B, Dey A, Mahajan D, Menzies R, McIntyre PB. Immunisation coverage annual report, 2009. Commun Dis Intell. 2011;35:132-48.

54. Misegades LK, Winter K, Harriman K, Talarico J, Messonnier NE, Clark TA, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. Journal of the American Medical Association. 2012;308:2126-32.

55. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med. 2012;367:1012-9.

56. de Greeff SC, Mooi FR, Westerhof A, Verbakel JM, Peeters MF, Heuvelman CJ, et al. Pertussis disease burden in the household: how to protect young infants. Clin Infect Dis. 2010 May 15;50(10):1339-45.

57. Wiley KE, Zuo Y, Macartney KK, PB M. Sources of pertussis infection in young infants: a review of key evidence informing targeting of the cocoon strategy. Vaccine. 2013;31:618-25.

58. Jardine A, Conaty SJ, Lowbridge C, Staff M, Vally H. Who gives pertussis to infants? Source of infection for laboratory confirmed cases less than 12 months of age during an epidemic, Sydney, 2009. Communicable Diseases Intelligence. 2010;34(2):116-21.

59. World Health Organization. Meeting of the Strategic Advisory Group of Experts on immunization, April 2010 - conclusions and recommendations. Wkly Epidemiol Rec. 2010;85:197-212.

60. Quinn H, McIntyre P. The impact of adolescent pertussis immunization, 2004–2009: lessons from Australia. Bull World Health Organ. 2011;89:666-74.

61. Rank C, Quinn H, McIntyre P. Pertussis vaccine effectiveness after mass

immunization of high school students in Australia. The Pediatric Infectious Disease Journal. 2009;28(2):152-5.

62. Skoff T, Cohn A, Clark T, Messonier N, S M. Early impact of the US Tdap vaccination program on pertussis trends. Arch Pediatr Adolesc Med. 2012;166(4):344-9.

63. Skowronski DM, Janjua NZ, Sonfack Tsafack EP, Ouakki M, Hoang L, De Serres G. The number needed to vaccinate to prevent infant pertussis hospitalization and death through parent cocoon immunization. Clinical Infectious Diseases. 2012 February 1, 2012;54(3):318-27.

64. Australian Government Department of Health and Ageing. ATAGI bulletin 44th meeting: 24-25 February 2011. [Internet] Canberra: Australian Government Department of Health and Ageing; 2011 [cited 2013 September 20]; Available from: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/atagi-meet44bulletin.

# APPENDIX

## Appendix 5.A. Age-specific pertussis notifcation and hospitalisation rates per 100,000 population for each state and territory, Australia, 2006–2012*

| State or territory | | Age group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <6mo | 6mo-4yo | 5-9yo | 10-14yo | 15-19yo | 20-64yo | ≥65 |
| **ACT** | | | | | | | | |
| **2006** | **Notifications** | 0.0 | 32.4 | 29.2 | 9.3 | 36.7 | 94.4 | 100.4 |
| | **Hospitalisations** | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.5 | 0.0 |
| **2007** | **Notifications** | 43.9 | 15.5 | 4.9 | 0.0 | 27.9 | 32.8 | 39.2 |
| | **Hospitalisations** | 86.8 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **2008** | **Notifications** | 87.1 | 25.1 | 58.6 | 47.1 | 23.5 | 41.6 | 46.7 |
| | **Hospitalisations** | 86.9 | 0.0 | 0.0 | 0.0 | 0.0 | 1.8 | 2.9 |
| **2009** | **Notifications** | 247.8 | 78.3 | 82.4 | 51.9 | 46.9 | 104.4 | 143.5 |
| | **Hospitalisations** | 371.7 | 4.9 | 0.0 | 0.0 | 0.0 | 0.9 | 5.6 |
| **2010** | **Notifications** | 159.1 | 99.3 | 503.5 | 377.1 | 74.4 | 172.7 | 221.5 |
| | **Hospitalisations** | 156.0 | 9.3 | 0.0 | 0.0 | 0.0 | 1.3 | 5.4 |
| **2011** | **Notifications** | 320.6 | 171.4 | 363.7 | 343.2 | 104.0 | 201.6 | 333.5 |
| **2012** | **Notifications** | 78.0 | 62.4 | 130.7 | 247.9 | 66.3 | 106.5 | 153.2 |
| **Average rate notifications** | | 137.0 | 71.2 | 169.2 | 152.4 | 54.2 | 109.1 | 153.4 |
| **Average rate hospitalisations** | | 144.0 | 3.0 | 0.0 | 0.0 | 0.0 | 0.9 | 2.9 |

*Hospitalisation data available through 2010.

| State or territory | | Age group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <6mo | 6mo-4yo | 5-9yo | 10-14yo | 15-19yo | 20-64yo | ≥65 |
| NSW | | | | | | | | |
| 2006 | Notifications | 161.4 | 27.4 | 13.4 | 18.7 | 35.2 | 64.1 | 60.5 |
| | Hospitalisations | 176.9 | 7.4 | 0.7 | 1.1 | 0.2 | 1.2 | 5.0 |
| 2007 | Notifications | 137.7 | 28.1 | 24.2 | 18.3 | 17.9 | 23.1 | 22.3 |
| | Hospitalisations | 109.1 | 5.1 | 0.5 | 0.0 | 0.0 | 0.3 | 2.0 |
| 2008 | Notifications | 571.7 | 233.3 | 278.9 | 270.1 | 135.7 | 65.9 | 50.4 |
| | Hospitalisations | 456.8 | 16.3 | 3.0 | 0.7 | 1.3 | 1.4 | 3.6 |
| 2009 | Notifications | 911.2 | 579.4 | 605.0 | 342.0 | 141.1 | 97.2 | 63.1 |
| | Hospitalisations | 728.3 | 28.0 | 3.4 | 3.8 | 1.7 | 2.0 | 8.3 |
| 2010 | Notifications | 418.2 | 284.1 | 626.2 | 365.0 | 88.3 | 62.9 | 44.9 |
| | Hospitalisations | 285.8 | 12.1 | 3.2 | 0.9 | 0.6 | 1.9 | 4.1 |
| 2011 | Notifications | 648.9 | 492.4 | 931.1 | 526.2 | 77.2 | 77.0 | 55.3 |
| 2012 | Notifications | 337.2 | 239.2 | 343.6 | 205.2 | 33.3 | 38.3 | 32.4 |
| Average rate notifications | | 459.8 | 273.2 | 403.3 | 248.1 | 75.8 | 61.3 | 46.8 |
| Average rate hospitalisations | | 355.0 | 13.9 | 2.1 | 1.3 | 0.8 | 1.4 | 4.6 |

| State or territory | | Age group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <6mo | 6mo-4yo | 5-9yo | 10-14yo | 15-19yo | 20-64yo | ≥65 |
| NT | | | | | | | | |
| 2006 | Notifications | 109.2 | 6.3 | 0.0 | 0.0 | 64.4 | 59.0 | 51.3 |
| | Hospitalisations | 163.8 | 6.3 | 0.0 | 0.0 | 0.0 | 3.0 | 10.3 |
| 2007 | Notifications | 53.9 | 12.5 | 5.8 | 0.0 | 0.0 | 13.1 | 48.2 |
| | Hospitalisations | 54.0 | 6.2 | 0.0 | 0.0 | 0.0 | 0.7 | 0.0 |
| 2008 | Notifications | 880.6 | 277.5 | 368.1 | 317.9 | 121.9 | 176.0 | 275.7 |
| | Hospitalisations | 827.1 | 49.6 | 5.7 | 0.0 | 12.1 | 2.1 | 9.2 |
| 2009 | Notifications | 465.8 | 126.3 | 137.5 | 119.7 | 42.0 | 87.7 | 61.0 |
| | Hospitalisations | 619.5 | 12.1 | 5.7 | 0.0 | 5.9 | 1.4 | 0.0 |
| 2010 | Notifications | 317.5 | 172.4 | 315.0 | 194.0 | 90.4 | 116.2 | 164.8 |
| | Hospitalisations | 690.8 | 6.0 | 5.7 | 0.0 | 5.9 | 4.7 | 8.2 |
| 2011 | Notifications | 597.8 | 197.9 | 535.0 | 448.5 | 61.9 | 86.7 | 210.7 |
| 2012 | Notifications | 452.0 | 196.4 | 377.2 | 300.8 | 36.9 | 80.4 | 71.7 |
| Average rate notifications | | 414.5 | 142.6 | 249.5 | 196.7 | 59.9 | 89.1 | 127.8 |
| Average rate hospitalisations | | 476.9 | 16.0 | 3.4 | 0.0 | 4.9 | 2.4 | 5.5 |

| State or territory | | Age group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <6mo | 6mo-4yo | 5-9yo | 10-14yo | 15-19yo | 20-64yo | >65 |
| Qld | | | | | | | | |
| 2006 | Notifications | 61.6 | 13.7 | 8.3 | 36.9 | 47.6 | 55.8 | 95.7 |
| | Hospitalisations | 50.8 | 2.9 | 0.4 | 0.3 | 0.0 | 1.9 | 7.1 |
| 2007 | Notifications | 52.9 | 7.3 | 6.8 | 11.7 | 31.7 | 37.7 | 79.0 |
| | Hospitalisations | 52.7 | 1.2 | 0.7 | 1.0 | 0.3 | 1.5 | 4.5 |
| 2008 | Notifications | 147.6 | 28.0 | 26.4 | 39.3 | 38.3 | 51.7 | 96.7 |
| | Hospitalisations | 120.0 | 2.7 | 0.4 | 0.3 | 0.7 | 1.2 | 7.5 |
| 2009 | Notifications | 404.7 | 136.8 | 181.2 | 162.0 | 101.3 | 132.4 | 170.7 |
| | Hospitalisations | 353.8 | 14.0 | 2.8 | 2.4 | 1.0 | 3.1 | 9.1 |
| 2010 | Notifications | 471.7 | 179.6 | 334.4 | 262.1 | 102.9 | 163.1 | 210.7 |
| | Hospitalisations | 353.1 | 12.2 | 2.8 | 2.0 | 1.0 | 2.9 | 11.3 |
| 2011 | Notifications | 488.2 | 263.2 | 471.8 | 404.6 | 105.4 | 152.9 | 191.6 |
| 2012 | Notifications | 344.6 | 233.6 | 397.6 | 339.6 | 74.6 | 119.4 | 176.9 |
| Average rate notifications | | 287.6 | 127.9 | 207.9 | 180.0 | 72.3 | 103.2 | 148.6 |
| Average rate hospitalisations | | 193.0 | 6.9 | 1.4 | 1.2 | 0.6 | 2.1 | 8.0 |

| State or territory | | Age group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <6mo | 6mo-4yo | 5-9yo | 10-14yo | 15-19yo | 20-64yo | ≥65 |
| SA | | | | | | | | |
| 2006 | Notifications | 11.1 | 7.4 | 19.9 | 26.5 | 83.0 | 174.4 | 169.9 |
| | Hospitalisations | 44.4 | 4.9 | 1.0 | 1.0 | 2.9 | 4.0 | 11.0 |
| 2007 | Notifications | 0.0 | 14.7 | 7.4 | 9.9 | 16.0 | 28.5 | 26.2 |
| | Hospitalisations | 10.6 | 2.4 | 2.1 | 0.0 | 0.0 | 1.2 | 2.5 |
| 2008 | Notifications | 163.3 | 51.4 | 74.3 | 74.7 | 57.0 | 97.6 | 113.8 |
| | Hospitalisations | 192.3 | 3.6 | 1.1 | 1.0 | 1.0 | 2.4 | 6.1 |
| 2009 | Notifications | 847.8 | 338.6 | 602.2 | 582.7 | 181.8 | 313.7 | 247.9 |
| | Hospitalisations | 673.1 | 26.7 | 12.7 | 6.0 | 2.0 | 7.6 | 18.5 |
| 2010 | Notifications | 1119.3 | 493.1 | 1117.4 | 872.4 | 238.1 | 392.6 | 334.6 |
| | Hospitalisations | 794.4 | 39.5 | 9.6 | 14.0 | 6.0 | 7.9 | 25.1 |
| 2011 | Notifications | 277.2 | 212.2 | 244.9 | 191.1 | 58.5 | 132.2 | 137.8 |
| 2012 | Notifications | 108.1 | 50.5 | 127.9 | 93.6 | 21.9 | 46.4 | 52.1 |
| Average rate notifications | | 366.0 | 169.9 | 310.7 | 263.5 | 94.1 | 169.8 | 154.4 |
| Average rate hospitalisations | | 352.5 | 15.9 | 5.3 | 4.4 | 2.4 | 4.7 | 12.8 |

| State or territory | | Age group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <6mo | 6mo-4yo | 5-9yo | 10-14yo | 15-19yo | 20-64yo | ≥65 |
| Tas | | | | | | | | |
| 2006 | Notifications | 62.8 | 3.7 | 0.0 | 11.7 | 0.0 | 8.7 | 12.6 |
| | Hospitalisations | 31.4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.4 |
| 2007 | Notifications | 30.2 | 7.3 | 3.2 | 2.9 | 2.9 | 4.5 | 8.2 |
| | Hospitalisations | 0.0 | 3.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 2008 | Notifications | 303.9 | 70.8 | 60.7 | 83.2 | 58.4 | 28.0 | 26.7 |
| | Hospitalisations | 180.1 | 10.4 | 0.0 | 0.0 | 0.0 | 0.3 | 1.3 |
| 2009 | Notifications | 722.1 | 224.3 | 162.1 | 211.3 | 134.5 | 107.4 | 57.0 |
| | Hospitalisations | 295.7 | 23.5 | 0.0 | 0.0 | 2.9 | 2.7 | 3.9 |
| 2010 | Notifications | 258.5 | 82.5 | 62.0 | 54.2 | 67.3 | 51.9 | 39.0 |
| | Hospitalisations | 320.4 | 6.6 | 0.0 | 0.0 | 2.9 | 0.0 | 1.3 |
| 2011 | Notifications | 256.2 | 114.9 | 156.1 | 197.8 | 26.5 | 51.7 | 41.4 |
| 2012 | Notifications | 1328.3 | 677.7 | 786.9 | 691.2 | 130.0 | 141.7 | 111.0 |
| Average rate notifications | | 422.4 | 171.1 | 173.9 | 175.3 | 60.0 | 56.7 | 43.9 |
| Average rate hospitalisations | | 164.7 | 9.1 | 0.0 | 0.0 | 1.2 | 0.6 | 1.6 |

| State or territory | | Age group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <6mo | 6mo-4yo | 5-9yo | 10-14yo | 15-19yo | 20-64yo | ≥65 |
| Vic | | | | | | | | |
| 2006 | Notifications | 30.7 | 2.8 | 3.7 | 6.2 | 15.5 | 23.7 | 32.8 |
| | Hospitalisations | 67.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.3 | 2.5 |
| 2007 | Notifications | 58.8 | 14.5 | 13.1 | 17.6 | 17.8 | 21.3 | 21.2 |
| | Hospitalisations | 81.6 | 2.1 | 0.3 | 0.0 | 0.0 | 0.5 | 1.3 |
| 2008 | Notifications | 141.3 | 25.5 | 25.9 | 41.6 | 20.7 | 34.0 | 28.6 |
| | Hospitalisations | 134.6 | 4.7 | 0.3 | 0.3 | 0.6 | 0.8 | 1.8 |
| 2009 | Notifications | 302.3 | 74.8 | 72.4 | 81.1 | 43.5 | 68.7 | 72.0 |
| | Hospitalisations | 328.8 | 4.8 | 0.9 | 1.2 | 0.3 | 1.2 | 3.5 |
| 2010 | Notifications | 470.3 | 133.7 | 207.6 | 256.3 | 75.6 | 113.1 | 119.5 |
| | Hospitalisations | 437.5 | 8.2 | 3.0 | 0.9 | 1.1 | 2.3 | 7.7 |
| 2011 | Notifications | 434.8 | 189.7 | 282.3 | 263.3 | 75.4 | 134.0 | 164.1 |
| 2012 | Notifications | 232.9 | 98.9 | 106.6 | 95.6 | 31.2 | 70.0 | 101.7 |
| Average rate notifications | | 241.8 | 79.5 | 102.5 | 108.2 | 40.1 | 67.5 | 79.3 |
| Average rate hospitalisations | | 212.4 | 4.1 | 0.9 | 0.5 | 0.4 | 1.1 | 3.4 |

| State or territory | | Age group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | <6mo | 6mo-4yo | 5-9yo | 10-14yo | 15-19yo | 20-64yo | ≥65 |
| WA | | | | | | | | |
| 2006 | Notifications | 66.9 | 17.1 | 10.3 | 5.6 | 12.3 | 13.1 | 13.2 |
| | Hospitalisations | 74.3 | 4.3 | 0.0 | 0.0 | 0.0 | 0.1 | 0.0 |
| 2007 | Notifications | 7.0 | 4.9 | 2.2 | 2.8 | 5.3 | 7.2 | 7.2 |
| | Hospitalisations | 13.8 | 1.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.8 |
| 2008 | Notifications | 198.2 | 30.6 | 20.9 | 10.3 | 10.5 | 20.2 | 24.9 |
| | Hospitalisations | 184.1 | 3.9 | 0.0 | 0.0 | 0.0 | 0.4 | 0.8 |
| 2009 | Notifications | 240.7 | 53.1 | 58.4 | 31.2 | 17.4 | 31.2 | 30.8 |
| | Hospitalisations | 201.1 | 8.2 | 0.7 | 0.7 | 0.0 | 0.7 | 0.4 |
| 2010 | Notifications | 313.0 | 89.3 | 122.4 | 118.5 | 40.1 | 49.7 | 59.3 |
| | Hospitalisations | 239.2 | 7.2 | 1.4 | 1.3 | 0.0 | 1.2 | 2.9 |
| 2011 | Notifications | 610.9 | 285.9 | 520.3 | 474.1 | 71.7 | 108.4 | 116.8 |
| 2012 | Notifications | 375.7 | 284.0 | 247.9 | 263.1 | 63.7 | 104.5 | 144.5 |
| Average rate notifications | | 267.2 | 116.4 | 145.1 | 131.2 | 31.9 | 49.9 | 60.0 |
| Average rate hospitalisations | | 145.9 | 5.2 | 0.4 | 0.4 | 0.0 | 0.5 | 1.0 |

# CHAPTER 6. EVALUATION OF A SURVEILLANCE SYSTEM

## Australian post-licensure surveillance for intussusception associated with receipt of rotavirus vaccines

# TABLE OF CONTENTS

# PREFACE

## Background and scope of the chapter

Because of a demonstrated risk of intussusception (IS) associated with the first rotavirus vaccine, RotaShield, the World Health Organization (WHO) recommended post-licensure safety surveillance when Rotarix and RotaTeq rotavirus vaccines were introduced in the mid-2000s.

To accomplish IS surveillance in Australia, an ad hoc combination of four different surveillance systems emerged somewhat organically. Nonetheless, the strategy was effective, achieving both IS surveillance and identifying a small IS risk associated with receipt of both vaccines.

The National Centre for Immunisation Research and Surveillance (NCIRS) recognised evaluating this non-traditional surveillance effort would be constructive. By highlighting the contribution of each surveillance system and the efficacy of combining them, future surveillance efforts might be better structured and designed to include multiple surveillance components. NCIRS invited me to conduct this evaluation. It is included in its entirety in this chapter.

## Investigatory role

I was responsible for all aspects of this evaluation, including format design, determining the evidence needed to assess this non-traditional surveillance system, compiling this evidence and then conducting the analysis. An abstract regarding the evaluation was accepted for an oral presentation at the 7th Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) Bi-regional Scientific Conference (Appendix 6.F), and I was fortunate to travel to Vietnam to present my preliminary results to an international audience.

## Lessons learned

Structuring this evaluation was challenging. Because of the non-traditional nature of the surveillance system, determining exactly the evaluation's limits and scope, and how to best assess the relative strengths and weaknesses of the contributing surveillance systems was problematic. This was positive, however; it forced me to better comprehend concepts like sensitivity and predictive value positive (PPV). It impressed upon me that these are more than surveillance system attributes. Rather, they represent complex trade-offs, which may require, for example, careful consideration of the costs involved with detecting too many false positives.

Conducting the evaluation involved seeking stakeholder feedback and to do this I distributed a questionnaire to 40 individuals and received six replies. I had been advised by NCIRS colleagues which stakeholders were the most appropriate to target and had knowledgeable NCIRS staff review the questionnaire. I believe that the low response rate was purely due to how busy the stakeholders were and that they did not value the purpose of the evaluation. While this was frustrating, it was an instructive experience. If I had the opportunity to re-do the evaluation, I would contact each stakeholder individually and seek to interview as many as possible. I believe this would likely yield better participation as well as richer qualitative data.

The evaluation also illuminated the complexity facing policy makers when assessing vaccine-associated risks and benefits. While IS can be a severe condition for young infants, the incidence of IS, whether vaccine-associated or not, is rare. Conversely, rotavirus infection represents a considerable burden of disease globally, including high mortality rates associated with the illness for children in developing nations.

Lastly, presenting the preliminary results of this evaluation at the TEHPINET Conference in Vietnam to an international audience was an invaluable experience. Moreover, with attendees hailing from a variety of countries, all with diverse specialities and frames of reference, it was a lesson in tailoring the messages of a presentation to the audience.

## Public health impact

In 2010 the Australian Government suspended the seasonal influenza vaccine for children aged <5 years due to increased febrile convulsions among this age group. An independent review led by Professor John Horvath ensued, the results of which were made public in 2011, with the final report suggesting that Australian adverse event following immunisation (AEFI) surveillance and response could be improved.

My evaluation of Australia's IS surveillance response—a novel method of AEFI surveillance—suggests a potential method of improvement. Until mine, no formal evaluation of this combinatorial IS response had been undertaken. My findings demonstrated that, despite being unplanned and somewhat ad hoc, by incorporating multiple surveillance systems it was capable of capitalising on the strengths of each. Furthermore, by formalising and publicising the effort's achievements, and thus increasing recognition of these successes amongst the relevant public health and vaccine safety authorities, it may be employed to inform future similar vaccine safety surveillance efforts. To this end, NCIRS will present the evaluation to the Department of Health (DOH), the Therapeutic Goods Administration (TGA) and the Advisory Committee on the Safety of Vaccines (ACSOV).

AEFI surveillance—in whatever manifestation—is a key component in ensuring and maintaining confidence in vaccines. This is particularly important for rotavirus vaccines. Given the legacy of the RotaShield vaccine, IS monitoring is imperative to help guarantee that rotavirus vaccines remain available and affordable for all children—especially those in developing nations.

## Acknowledgements

Associate Professor Kristine Macartney of NCIRS assisted with this evaluation by helping me to put together the pieces of Australia's rotavirus vaccine surveillance story. Additionally, she was instrumental in advising on the appropriate stakeholders to include in the evaluation and in helping access them. Finally, she patiently reviewed and provided feedback, not only on the evaluation, but also the stakeholder

questionnaire and my TEPHINET abstract and presentation. Also of NCIRS, Dr Deepika Mahajan answered questions regarding the TGA's Adverse Drug Reaction Reporting System (ADRS).

Various members of Australian Committee on the Safety of Medicines (ACSOM), ACSOV, and Australian Technical Advisory Group on Immunisation (ATAGI) took time to respond to the stakeholder questionnaire.

As with all of my work, my supervisors Drs Helen Quinn and Martyn Kirk provided guidance and feedback on the evaluation as well as the TEPHINET abstract and presentation. Dr Stephanie Davis also reviewed my presentation.

Additionally, I would like to thank the Australian National University's (ANU) National Centre for Epidemiology and Population Health (NCEPH) for funding my attendance at the TEPHINET Conference and facilitating a fantastic opportunity to present my work to an international audience.

Finally, I would like to thank the TGA for use of ADRS data and co-investigators involved in the Australian national Paediatric Active Enhanced Disease Surveillance (PAEDS) network (Peter Richmond, Christopher Blyth, Helen Marshall, Michael Gold, Nigel Crawford, Jenny Royle, Jim Buttery, Elizabeth Elliott, Robert Booy and Yvonne Zurynski) for their cooperation in allowing data from PAEDS to be included in this evaluation. Additionally, I would like to thank the Australian Paediatric Surveillance Unit (APSU) for the use of its data. Finally, I wish to acknowledge the New South Wales (NSW) Health Admitted Patient Data Collection as well as all staff who conducted chart reviews and data extraction which were used in components of this evaluation.

# ABBREVIATIONS

| | |
|---|---|
| **ACIP** | Advisory Committee on Immunization (US) |
| **ACIR** | Australian Childhood Immunisation Register |
| **ACSOM** | Advisory Committee on the Safety of Medicines |
| **ACSOV** | Advisory Committee on the Safety of Vaccines |
| **ACT** | Australian Capital Territory |
| **ADRS** | Adverse Drug Reaction Reporting System |
| **AEFI** | Adverse Event Following Immunisation |
| **AIHW** | Australian Institute of Health & Welfare |
| **ANU** | The Australian National University |
| **APSU** | Australian Paediatric Surveillance Unit |
| **ATAGI** | Australian Technical Advisory Group on Immunisation |
| **CDC** | Centers for Disease Control & Prevention (US) |
| **CDI** | *Communicable Diseases Intelligence* (Journal) |
| **CHW** | The Children's Hospital at Westmead |
| **CI** | Confidence Interval |
| **DAEN** | Database of Adverse Event Notifications |
| **DOH** | Department of Health |
| **DOHA** | Department of Health and Ageing |
| **ED** | Emergency Department |

| | |
|---|---|
| **FDA** | Food & Drug Administration (US) |
| **GP** | General Practice |
| **ICD** | International Statistical Classification of Diseases & Related Health Problems |
| **IS** | Intussusception |
| **MAE** | Master of Philosophy Applied Epidemiology |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MMR** | Measles-Mumps-Rubella (vaccine) |
| **NCEPH** | National Centre for Epidemiology & Population Health |
| **NCIRS** | National Centre for Immunisation Research & Surveillance |
| **NIP** | National Immunisation Program |
| **NSW** | New South Wales |
| **PAEDS** | Paediatric Active Enhanced Disease Surveillance System |
| **PHAA** | Public Health Association of Australia |
| **PPV** | Positive Predictive Value |
| **SCCS** | Self-Controlled Case Series |
| **TEPHINET** | Training Programs in Epidemiology & Public Health Interventions Network |
| **TGA** | Therapeutic Goods Administration |
| **VAERS** | Vaccine Adverse Events Reporting System (US) |
| **VSD** | Vaccine Safety Database (US) |
| **WHO** | World Health Organization |

# LIST OF TABLES

# LIST OF FIGURES

# ABSTRACT

## Introduction

Rotashield was the first available rotavirus vaccine. Its use, however, was problematic; increased IS risk led to withdrawal from American usage in 1999. In 2007, when two new rotavirus vaccines were introduced worldwide, Australia employed specific IS surveillance mechanisms beyond just passive AEFI reporting. This study evaluated the systems used to determine if such a mixed surveillance model could be considered for other new vaccines.

## Methods

Australia's IS surveillance was evaluated using WHO and Centers for Disease Control and Prevention (CDC) frameworks. All four contributing surveillance mechanisms (the TGA's passive ADRS; APSU; PAEDS system; and hospitalisation inpatient databases) were assessed for data quality, timeliness, sensitivity, PPV, causality ascertainment, representativeness and usefulness.

## Results

National passive ADRS surveillance was well-established but insensitive—detecting 44 IS cases compared with 79 by APSU and 251 by PAEDS. These active systems, although providing greater clinical data including medical history and vaccination status confirmation, were not instituted prior to vaccine introduction. As these active systems were sentinel, some IS cases may not have been detected. International Statistical Classification of Diseases and Related Health Problems (ICD) coded cases from hospitalisation inpatient databases were representative, and data analysis was aided by using Brighton Collaboration criteria. Case review, however, was labour-intensive.

## Conclusion

Passive surveillance alone was unlikely to detect increased IS risk associated with current rotavirus vaccines. Active surveillance was critical in evaluating IS risk and led

to the first published study of IS risk associated with the new rotavirus vaccines. Data analysis from large inpatient databases also contributed significantly. This experience demonstrates that AEFI surveillance reliant upon multiple surveillance mechanisms is effective and this model may be adapted to other new vaccines. Such a model, however, could benefit from improved planning and coordination.

# EVALUATION OF AUSTRALIAN POST-LICENSURE SURVEILLANCE FOR INTUSSUSCEPTION ASSOCIATED WITH RECEIPT OF ROTAVIRUS VACCINES

**Ms Alexis Pillsbury**[1,2], Master of Philosophy (Applied Epidemiology) Scholar

Affiliation(s)

1. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), The Children's Hospital at Westmead and the University of Sydney, New South Wales, Australia.
2. National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australia.

# INTRODUCTION

This report evaluates Australia's effort to conduct post-licensing surveillance for IS following the introduction of the RotaTeq and Rotarix rotavirus vaccines in 2007. Safety monitoring was necessary due to a link confirmed in 1998 between receipt of RotaShield, the first licensed rotavirus vaccine, and an increased IS risk. [1]

The evaluation begins with a brief overview of the public health importance of both IS and rotavirus gastroenteritis in Australia and globally, followed by a summary of the RotaShield incident and its impact on the next generation of rotavirus vaccines. It then describes the Australian IS surveillance system that evolved, consisting of four contributing surveillance systems. It evaluates specific attributes of each system using an amalgamation of WHO and US CDC evaluation tools.[2-4] Finally, it considers the efficacy of the system as a whole for detecting IS as an AEFI, and whether it succeeded in achieving its surveillance objectives.

# OVERVIEW: THE PUBLIC HEALTH IMPORTANCE OF ROTAVIRUS AND INTUSSUSCEPTION

## Rotavirus

Globally, rotavirus is the most common cause of severe gastroenteritis for infants and children <5 years of age. Compared with other causes of diarrhoea, rotavirus-associated diarrhoea is responsible for higher dehydration and hospitalisation rates,[5] contributing annually to approximately 23 million outpatient visits, 2.3 million hospitalisations, and over half a million deaths. Eighty-five percent of deaths occur in developing countries.[6]

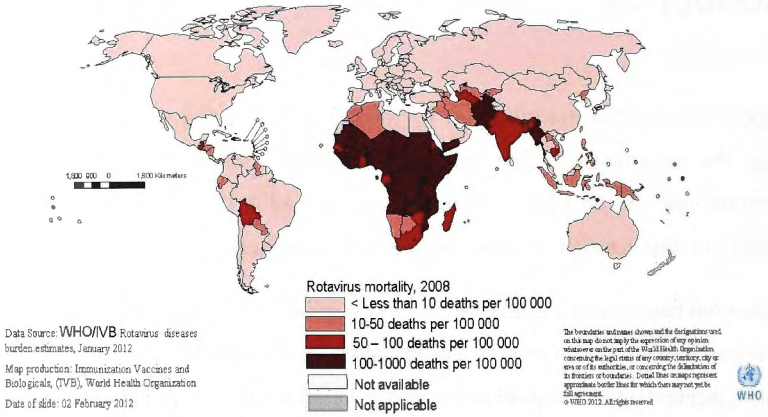



**Figure 6.1. Global rotavirus mortality rates per 100,000 population for children <5 years of age, 2008[7]**

Worldwide, most children experience an episode of rotavirus gastroenteritis by their fifth birthday.[6] Because rotavirus is highly prevalent, improving sanitation and hygiene does not equate to reduced transmission; effective vaccines are thus the primary source of prevention.[6]

In Australia, before the introduction of the rotavirus vaccines in the mid-2000s, rotavirus gastroenteritis comprised an estimated 10,000 hospitalisations, 22,000 Emergency Department (ED) presentations and 115,000 visits to a general practice (GP) physician for children <5 years of age,[8] with one death per year attributed to the virus.[5, 9] Noticeably higher rates of severe disease afflicted Indigenous populations, with infant hospitalisation rates five times those of non-Indigenous populations.[5] Annually, Australian costs associated with rotavirus were estimated at $30 million.[8]

Following the introduction of the rotavirus vaccines in Australia, a sustained decrease in rotavirus hospitalisations was observed for the 2008 and 2009 seasons. Though a 75% reduction was observed across all age groups—suggesting a positive impact on herd immunity—the reduction was particularly prevalent for infants: a 93% reduction compared with the six years prior to vaccine introduction.[9] At the global level, a 2010 systematic review of published efficacy and effectiveness trials of rotavirus vaccines

estimated that RotaTeq and Rotarix could prevent 74% (95% Confidence Interval (CI): 35–90%) of rotavirus deaths and 47–57% of rotavirus hospitalisations.[10]

## Intussusception

The most common cause of bowel obstruction in infants and young children, IS is the invagination of a segment of proximal bowel into a more distal portion resulting in intestinal obstruction. IS is an uncommon event, estimated at less than one per 1,000 live births in many developed countries.[11] In most cases, the cause of the IS remains unknown.[12, 13]

Diagnosis of IS includes identifying invagination of the intestine using contrast enema (air or liquid), ultrasound or surgery.[14] Without prompt treatment, bleeding and/or intestinal perforation can occur and may be life threatening, although IS deaths are rare in the developed world.[11] In developing countries with limited resources and medical expertise, however, mortality has been estimated at more than 20%.[12]

There is no known association between naturally occurring rotavirus infection and IS; there is, however, an established risk associated with the rotavirus vaccine and IS which will be subsequently detailed. Nonetheless, the precise mechanism is not wholly understood. Regionally, because the incidence of IS varies significantly, with countries like Vietnam and China reporting much higher rates,[11] it has been postulated that there may be 'genetic, ethnic, infectious or environmental factors' which contribute to IS. No conclusive evidence, however, has confirmed this.[11] Baseline IS data from most developing countries are lacking.[15, 16]

In Australia, between 1994 and 2000, there were approximately 1,794 IS hospitalisations in infants and one reported death.[11] Rates among Indigenous Australian infants are lower than those observed in non-Indigenous infants.[11]

Compared with the burden of rotavirus gastroenteritis, the burden of IS is considerably lower in both developed and developing countries.

## The RotaShield incident and its legacy

The first rotavirus vaccine, RotaShield (Wyeth-Lederle), was licensed in 1998. RotaShield was a tetravalent rhesus rotavirus vaccine that had been demonstrated safe in clinical trials conducted in the US, Finland and Venezuela. In these trials, RotaShield was shown to prevent more than 90% of hospital admissions due to rotavirus diarrhoea in the US and 79% in Venezuela.[17]

Nine months after licensing RotaShield, the US CDC reported an increase in IS cases following receipt of RotaShield as detected by their passive surveillance system, the Vaccine Adverse Events Reporting System (VAERS). Between September 1998 and July 1999, 15 cases among infants who had received RotaShield were reported compared to four IS reports in the previous seven years.[18] Studies determined that the risk associated with RotaShield resulted in one excess case of IS per approximately 5,000–10,000 children vaccinated.[19]

Subsequent research confirmed the causal relationship between receipt of RotaShield vaccination and IS; RotaShield was consequently removed from the market before ever having been introduced in any other countries.[16, 20] This was a disappointing setback to advancing the fight against rotavirus which was far more prevalent than IS.

Despite this setback, because rotavirus gastroenteritis was responsible for such extensive and costly morbidity and mortality for infants and young children globally[10, 17], a strong impetus to develop a safe alternative vaccine persisted. Efforts resulted in two new rotavirus vaccines being developed and introduced for use in the mid-2000s: RotaTeq (Merck) and Rotarix (GlaxoSmithKline). Both vaccines underwent pre-licensure clinical trials in the US, Finland and Latin American countries. Trials were designed to be large enough to detect a risk of IS similar to that which had been identified with the RotaShield vaccine. No increased risk was observed in any clinical trial.

**Table 6.1. History and overview of licensed rotavirus vaccines[6, 21]**

| Vaccine | RotaShield | Rotarix | RotaTeq |
|---|---|---|---|
| **Licensed date** | 1998 (only released in US) | 2006 (registered in Australia; included in NIP* from 2007) | 2006 (registered in Australia; included in NIP from 2007) |
| **Manufacturer** | Wyeth-Lederle Vaccines | GlaxoSmithKline | Merck |
| **Type of vaccine** | Tetravalent rhesus-human vaccine | Monovalent human vaccine containing G1p[8] strain (RV1) | Pentavalent human-bovine reassortant vaccine containing G1, G2, G3, G4 and P1a[8] strains (RV5) |
| **Recommended dosage** | 3 doses (2, 4, 6 months) | 2 doses (2, 4 months) | 3 doses (2, 4, 6 months) |
| **Status** | Withdrawn in 1999 | Currently in use | Currently in use |

*NIP: National Immunisation Program

Because of the legacy of the RotaShield vaccine, IS surveillance was acknowledged as an important accompaniment to the introduction of the new rotavirus vaccines. This surveillance recommendation was formalised by the WHO in 2009 when it officially endorsed routine rotavirus vaccination for all infants.[22]

Beyond the utility of IS monitoring to provide country level incidence data, safety monitoring was also desired for its contribution to the existing IS evidence base and for highlighting regional IS differences. Additionally, with the *Lancet*'s 1998 Wakefield publication (since retracted) linking the measles-mumps-rubella (MMR) vaccine to autism occurring at the same time as questions were raised about RotaShield safety, vaccine confidence had been negatively impacted. Safety monitoring has been critical for restoring and maintaining confidence, both from the perspective of the international health community and from the public. Moreover, documenting the safety and effectiveness of the rotavirus vaccines in developed nations plays an important role in ensuring that these much-needed vaccines remain available and affordable for low- and middle-income countries.

## Australian IS surveillance

Both RotaTeq and Rotarix vaccines were registered in Australia in 2006 and included in the National Immunisation Program (NIP) from 2007. Because of differing purchasing arrangements, states and territories were able to independently choose which vaccine to administer (Figure 6.2). This resulted in an approximately equal number of children receiving each vaccine.[16]

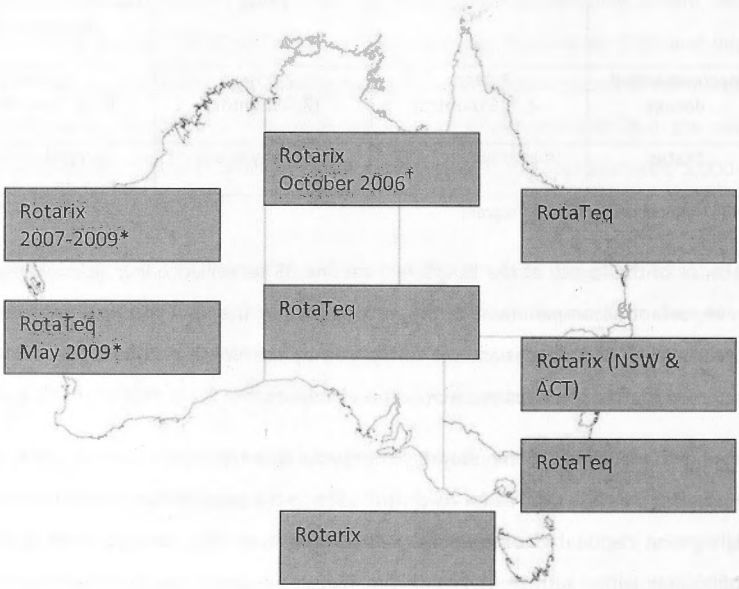



**Figure 6.2. Type of rotavirus vaccine used by each Australian state and territory**

***Western Australia: Dates are indicated because vaccine type was switched.**
**†Northern Territory: Date is indicated because vaccine was introduced earlier than in the other states/territories.**

No safety data existed outside of that available from the post-licensure clinical trials and consequently the recommended upper age limit for receiving the first dose of RotaTeq was 12.9 weeks and Rotarix was 14.9 weeks.[16] Between 1 July 2007 and 31 December 2008, 87% of all eligible infants was given at least one dose of a rotavirus vaccination and 84% of those completed two or three doses as advised by the relevant schedule.[16]

Because of the established link between RotaShield and IS, surveillance for IS commenced in July 2007 by the Australian Paediatric Surveillance Unit (APSU), a national active surveillance system which monitors rare childhood diseases. Relatively quickly, APSU was able to demonstrate a small but apparent association between IS and the new vaccines.[23] To determine the extent of the increased risk of IS, the Australian Government commissioned a series of research efforts. Though no formalised system specifically for monitoring IS incidence existed, nor a plan outlining how to conduct such surveillance, there were a variety of surveillance mechanisms which nonetheless could contribute information. Consequently, an 'organic' IS surveillance was activated utilising data from several surveillance systems (APSU; PAEDS; ADRS; hospitalisation inpatient databases) to capitalise on the strengths of each. Australia was one of the first countries to contribute comprehensive post-licensure research involving analyses of both new vaccines.

For the purposes of this evaluation, "surveillance system" will be used to refer to the four contributing systems when they are not referred to specifically by name. "IS surveillance" will be used to refer broadly to Australia's effort to conduct post-licensure safety surveillance relying on input from the four contributing systems.

## EVALUTION RATIONALE AND AIMS

Because none of the surveillance systems used for this post-licensure IS surveillance was established solely to monitor IS following rotavirus vaccination, each source had

its individual strengths and limitations when it came to doing so, and thus one system alone was assumed inadequate for thorough safety surveillance of this rare event. Moreover, the Australian Government desired more than signal detection or incidence rate estimates, knowing that case identification was necessary to assess thoroughly the association between the vaccines and IS. Though the merits of the individual surveillance systems used for IS surveillance had each been assessed to some extent, no efforts to date had considered whether or not post-licensure vaccine safety surveillance utilising multiple surveillance systems was a reliable method for monitoring a serious safety concern associated with the introduction of a new vaccine.

This evaluation described Australia's experience using multiple surveillance systems for conducting IS surveillance, and subsequently highlighted the lessons learned and recommendations. In light of the 2011 Horvath Review's recommendation for the evaluation of the benefits of additional surveillance mechanisms for AEFI detection,[24] this evaluation may have been particularly salient.

Specifically, this evaluation aimed to:

- describe the surveillance which evolved to monitor IS following receipt of the new rotavirus vaccines;
- assess the attributes of the individual surveillance systems used for IS surveillance;
- evaluate the usefulness and utility of the IS surveillance system; and
- identify whether or not the objectives of the IS surveillance were met.

# METHODS OF EVALUATION

This evaluation employed several evaluation frameworks created by the WHO and the US CDC, including:

- *Updated guidelines for evaluating public health surveillance systems* (2001; CDC)[3]
- *Post-marketing surveillance of rotavirus vaccine safety* (2009; WHO)[4]

Using guidance from an amalgamation of these frameworks, this evaluation described the IS surveillance, evaluated the attributes and utility of the contributing surveillance systems, and determined the efficacy of the IS surveillance. The four contributing surveillance systems were considered individually as well as how they functioned together to accomplish IS surveillance. As mentioned previously, the four surveillance systems included:

- the TGA's ADRS
- APSU
- PAEDS
- National and state/territory hospitalisation inpatient databases

## System description

Background information regarding the four surveillance systems used for the IS surveillance was obtained from the surveillance systems' websites, directly from the data custodians or through NCIRS. Where necessary, this included access to the raw data sets for relevant years. Additionally, several published and unpublished analyses and review papers describing the individual surveillance systems were readily available for consultation. Both the raw data sets and the written analyses contributed to the

evaluation of the attributes of each surveillance system individually and their collective utility.

Because of NCIRS's role in advising the Government about vaccine policy and practice, any information that was not available in written format was obtained through discussions with appropriate NCIRS staff who were involved both with the decision to add the rotavirus vaccines to the NIP and with the safety monitoring which subsequently occurred.

## Stakeholder involvement

Stakeholders were given a questionnaire seeking their observations and opinions regarding aspects of the IS surveillance. Staff at NCIRS who were knowledgeable about this assisted in identifying key stakeholders and reviewing the questionnaire. Stakeholders included members of ATAGI as well as members of ACSOV and ACSOM (Table 6.2). The questionnaire was distributed via email with two reminders sent. The questionnaire was distributed to 40 individuals and six replies were received. Questions were primarily open-ended and individuals were asked about the perceived objectives, management and outcomes of IS surveillance.

**Table 6.2. Identification and description of stakeholders questioned about the IS surveillance[25, 26]**

| Stakeholder group | Role of stakeholder group |
|---|---|
| Australian Technical Advisory Group on Immunisation (ATAGI) | Advises Minister for Health on the Immunise Australia Program and related issues |
| Advisory Committee on the Safety of Vaccines (ACSOV) | Provides advice and recommendations to the Minister for Health and the TGA on the safety, risk assessment and risk management of vaccines |
| Advisory Committee on the Safety of Medicines (ACSOM) | Provides advice and recommendations to the TGA on the safety, risk assessment and risk management of medicines. May also provide advice to the TGA on other matters related to the detection, assessment, understanding and prevention of adverse effects (pharmacovigilance) and any other matters referred to it by the TGA |

## Evaluation of attributes

As recommended by the CDC's *Updated guidelines for evaluating public health surveillance systems*[3], the following specific attributes outlined in Table 6.3 were assessed for each surveillance system which contributed to the IS surveillance.

**Table 6.3. Description of attributes evaluated for contributing surveillance systems**

| Attribute | Description |
|---|---|
| Data quality | The completeness and validity of the data |
| Timeliness | The time between steps in the data flow process into and out of the databases of each data source<br><br>Ability to be quickly implemented to achieve objectives of AEFI surveillance |
| Sensitivity | Ability to capture as many cases as possible; compared between sources |
| Causality ascertainment | Ability to provide information which supports a causality relationship between vaccination and IS |
| Positive Predictive Value (PPV) | The proportion of IS cases detected which are confirmed as true IS cases |
| Representativeness | Description of how representative detected IS cases are of IS cases in the wider population |

Not all attributes recommended by the CDC's *Updated guidelines for evaluating public health surveillance systems* were deemed useful or appropriate for this surveillance evaluation and several were therefore excluded. Causality ascertainment, though not an attribute included in the CDC guidelines, was included because it is an integral part of AEFI surveillance.[27]

All attributes were assessed by reviewing the published IS analyses and relevant literature, questioning individuals who work with the data, or accessing raw data sets. For sensitivity, this attribute was also assessed across the data sources by comparing IS cases detected by each. Similarly, PPV was also compared across data sources using Brighton Collaboration criteria definitions.[28] The Brighton Collaboration is an international voluntary network of health professionals who have developed standardised AEFI case definitions with the aim of improving quality and comparability of vaccine safety data.[29] A case which is a confirmed Brighton Level 1 has a high level of diagnostic certainty.

## Evaluation of utility

The CDC defines the utility or usefulness of a surveillance system by its contribution or value added, not merely by its ability to detect cases.[2, 3]

To determine the usefulness of the IS surveillance, the evaluation reviewed the system's objectives to assess whether or not these were met, and summarised the system's impact on and contribution to existing evidence, policy and practice.

# RESULTS

## Description of the IS surveillance

### *Purpose*

Because of the RotaShield experience, it was necessary to incorporate concurrent vaccine safety monitoring with the introduction of the new rotavirus vaccines. Though pre-licensure clinical trials of RotaTeq and Rotarix had not detected an increased risk of IS associated with vaccination, pre-licensure trials were designed to detect risks on a similar scale to what had been observed with the RotaShield vaccine. There was still the possibility that a smaller scale risk could have occurred. Moreover, as IS appears to vary substantially depending on region and demography, an increased risk could still have existed outside of the regions where the clinical trials were conducted. Additionally, the pre-licensure clinical trials involved administering the two vaccines according to strict age schedules, meaning that there was still the possibility that an increased IS risk could be apparent if the vaccines were administered at ages outside of these schedules.[14]

### *Objectives*

Because there was no one mechanism for conducting surveillance for IS occurring as an adverse event associated with vaccination, no pre-defined objectives existed for conducting this surveillance. When asked what the objectives of the IS surveillance were, no stakeholder (n=6) replying to the distributed questionnaire could confidently identify objectives. Answers included to monitor the number of IS hospital admissions; for APSU to monitor IS cases; for PAEDS to monitor admissions and patient outcomes. All respondents, however, were confident that surveillance was in place at the time the two vaccines were licensed. Additionally, when asked about who was in charge of coordinating and overseeing the IS surveillance effort which occurred with the introduction of the rotavirus vaccines, most stakeholders (n=5/6) who completed the questionnaire were unsure or attributed responsibility solely to either ADRS, APSU or PAEDS.

The WHO's *Post-marketing surveillance of rotavirus vaccine safety* states that the main objective of post-marketing surveillance should be to 'identify adverse events, and in particular rare or unanticipated adverse events, that may be associated with specific vaccines, to distinguish those that are causally related to vaccination and to estimate their incidence'.[4] In line with these guidelines, Australia's objectives for IS surveillance following the introduction of the rotavirus vaccines, though unspecified, included:

- Detecting all suspected IS cases;
- Identifying those cases for which a causal link could be identified with receipt of either rotavirus vaccine;
- Compiling thorough and useful case data when possible to contribute to the national epidemiological profile of IS, as the condition varies demographically and regionally;
- Compiling thorough and useful case data to inform incidence and risk analyses.

## Contributing surveillance systems: description, purpose, objectives

### *ADRS*

Historically, the only Australian system established for reporting vaccine related adverse events has been the TGA's passive system which has existed specifically for that purpose, with a formal database (ADRS) since 2000. Managed by the TGA's Office of Product Review, it records adverse events associated with immunisation and drug reactions reported by immunisation providers, healthcare professionals, vaccine manufacturers, parents and the public. Reported AEFI are assigned a causality rating which attempts to estimate the likelihood that the adverse event was caused by vaccination. AEFI are classified as 'serious' or 'non-serious'. Reactions are coded into standardised terms using the Medical Dictionary for Regulatory Activities (MedDRA).[30]

Until IS became a recognised adverse event associated with the rotavirus vaccines, the system would only have detected IS if it had occurred randomly as an adverse event associated temporally with another vaccine. A formal definition for IS was included in the system in 2006 when the rotavirus vaccines were registered.

The objective of ADRS is to 'detect early warning signals and generate hypotheses about possible new vaccine adverse events or changes in frequency of known ones'.[24] ADRS data are used for signal detection and de-identified data are routinely analysed and reported by NCIRS. Annual national surveillance summaries have been published in *Communicable Diseases Intelligence* (CDI) since 2002 and detail all valid reports where the vaccine cannot be excluded as cause of the adverse event due to biological implausibility.[30]

### *APSU*

The decision was made in 2007 to incorporate IS as a monitored condition into the already existing national APSU which had been partly funded by the Australian Government DOH since 1993 to conduct surveillance of rare childhood diseases. The

overarching objective of APSU is to guide clinical practice and education and to contribute to research.[31] APSU conditions are chosen in line with national research priorities and consequently a decision was made to include IS from May 2007–May 2010 to assist with the post-licensure safety surveillance of the new rotavirus vaccines. This was the first time that APSU had included an AEFI as one of its monitored conditions.

APSU surveillance relies on a network of approximately 1,250 paediatric clinicians reporting cases they have seen via monthly report cards. APSU follows up with clinicians to obtain more detail about individual cases. Data are housed within the Kids Research Institute at the Children's Hospital at Westmead (CHW). Data are released to investigators who collate, analyse and publish findings; study findings are reported every two years in the APSU Biennial Research Report. Research is also presented to ATAGI and other relevant groups when appropriate. APSU publishes annual reports detailing surveillance of monitored conditions that are communicable and vaccine preventable in CDI.

### *PAEDS*

PAEDS is a joint collaboration between APSU and NCIRS and was launched in 2007 to monitor cases of rare but serious vaccine related childhood conditions, including both vaccine preventable diseases and AEFI. PAEDS aims to detect conditions that other surveillance systems do not and to gather rich clinical data about cases to support research. IS was included as a PAEDS condition from its piloting stage.

The system utilises APSU and NCIRS infrastructures and unites experts from five major tertiary paediatric hospitals around Australia. Data are managed from a central database at the Kids Research Institute. PAEDS investigators access data for the purposes of conducting research.[32] Results are presented to relevant groups like ATAGI when appropriate.

### *Hospitalisation inpatient databases*

The fourth surveillance system utilised for IS surveillance was hospitalisation inpatient databases, both at the individual state/territory level (managed by the relevant health department) and at the national level (managed by the Australian Institute for Health and Welfare (AIHW)). The inpatient databases contain administrative, demographic and clinical information about patients admitted to public and private hospitals in Australia. They have been collated at a national level since 1993. Diagnoses and procedures are classified according to the International Statistical Classification of Diseases and related Health Problems (currently, Tenth Revision, Australian Modification (ICD-10-AM)). Though useful for IS surveillance, these data are collected for the purpose of planning health services, tracking indicators of health status, and providing statistical information to monitor the utilisation of state hospital services. They are collated at the national level for the purpose of collecting information about care provided to admitted patients in Australia hospitals.[33]

Table 6.4 summarises characteristics of these surveillance methods. Figure 6.3 demonstrates how a case of IS may be detected and reported and the interplay of the four surveillance systems. The appendices provide additional detail about how the contributing surveillance system functions individually.

**Table 6.4. Characteristics of surveillance systems contributing to the IS surveillance[30-33]**

| | ADRS | APSU | PAEDS | Hospitalisation data |
|---|---|---|---|---|
| **Description** | Records adverse events associated with immunisation and drug reactions | Records uncommon childhood diseases, complications of common diseases or adverse effects of treatment | Records uncommon, serious, vaccine-related childhood conditions | Record administrative, demographic and clinical information about patients admitted to public and private hospitals |
| **Reporting** | Passive<br><br>Reported by immunisation providers, healthcare professionals, vaccine manufacturers, parents and public | Passive<br><br>Reported by paediatricians | Active<br><br>Paediatric hospital-based surveillance | Data supplied by hospitals to state/territory health bodies; an aggregated de-identified minimum dataset is then submitted to AIHW |
| **Population under surveillance** | National; all ages | National; children <15 years<br><br>For IS surveillance children <24 months | CHW (Sydney); Royal Children's Hospital (Melbourne); Women's and Children's Hospital (Adelaide); Princess Margaret Hospital (Perth); Royal Children's Hospital (Brisbane)<br><br>Children <15 years<br><br>For IS surveillance, children <24 months | Both national and state/territory data include persons of all ages presenting to the majority of public and private hospitals nation-wide |

| | ADRS | APSU | PAEDS | Hospitalisation inpatient data |
|---|---|---|---|---|
| **Date established** | Data collected in formal database since 2000<br><br>Specific IS definition as AEFI included in database since 2006 when rotavirus vaccines registered | Established in 1993<br><br>IS from May 2007–May 2010 | Established in 2007<br><br>IS monitored from 2007 | National database established in 1993 |
| **Administered/ funded by** | TGA | DOH, CHW, RACP*, the University of Sydney, GlaxoSmithKline Australia (IS surveillance) | Joint initiative of APSU and NCIRS<br><br>Funded by the DOH | State/territory health departments and AIHW |
| **Output** | Annual surveillance summaries published in CDI<br><br>Data analysed routinely by NCIRS as part of its funding agreement with the DOH<br><br>3 months after report entered, data made available to public in the DAEN† | Findings reported every two years in the APSU Biennial Research Report<br><br>Surveillance of communicable and vaccine preventable diseases published every year since 2004 in CDI | Each condition under surveillance has a chief investigator and research group who analyse and report on findings | Most data published in reports and bulletins at both state/territory and national levels<br><br>Other data available to researchers subject to confidentiality and other guidelines |

*RACP: Royal Australasian College of Physicians
†DAEN: Database of Adverse Event Notifications

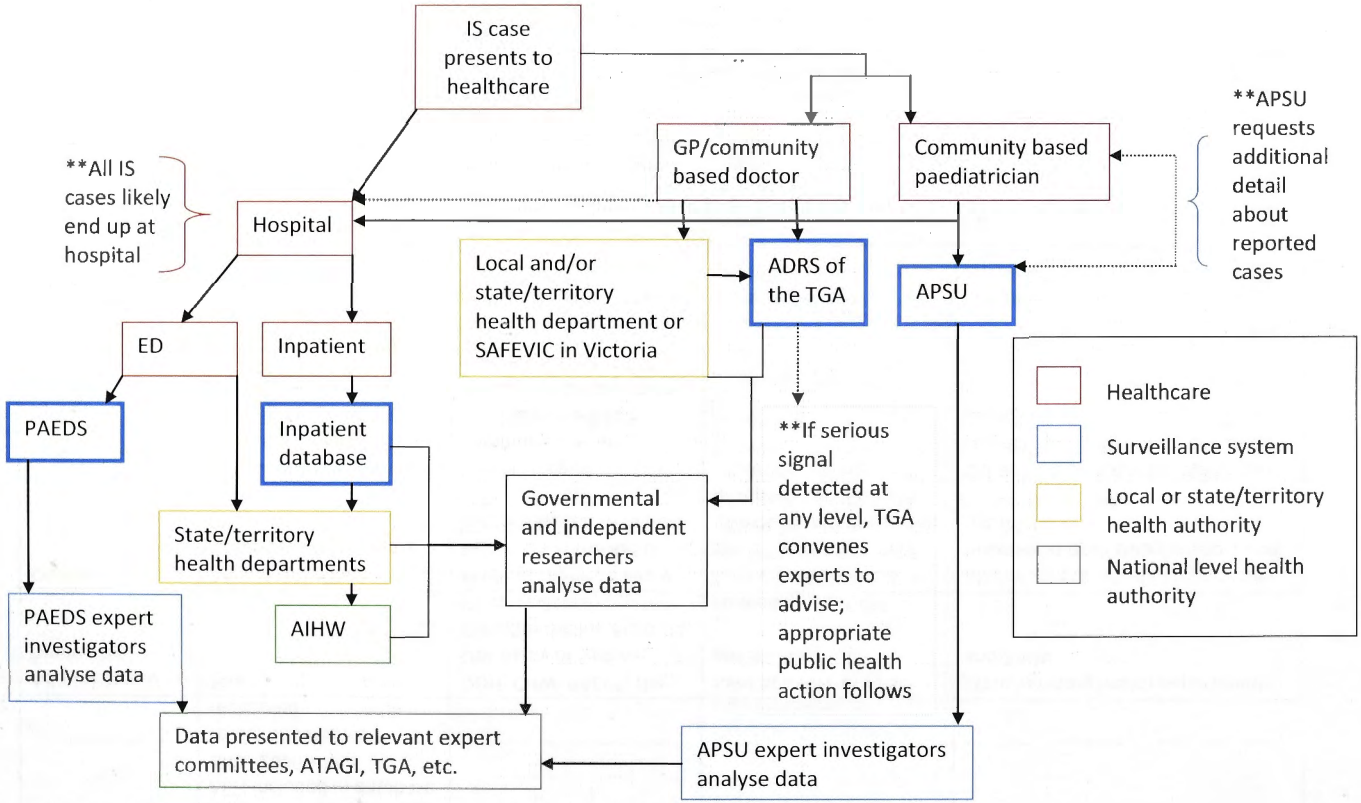



**Figure 6.3. How an IS case is detected/reported by the various contributing surveillance systems**

## Attributes

The following section details the strengths and limitations of each surveillance system by assessing its individual attributes—data quality; timeliness; sensitivity; causality ascertainment; positive predictive value; and representativeness—as outlined in Table 6.3. Within this section, although the strengths and limitations are referred to in the past tense, these surveillance systems are still currently operational.

### *Data quality*

Data quality referred to the completeness and validity of the data collected by each surveillance system.

In terms of contributing to IS surveillance, ADRS data quality was limited by variable completeness of information provided on individual data collection forms. Moreover, while national case definitions existed, reporting forms differed by state and territory resulting in compilation of slightly variant data. It is therefore likely that interpretation and application of these definitions varied at a state level, making analysis and case classification problematic. However, quality controls existed, with TGA medical officers undertaking weekly review of all reports, and bimonthly reviews of proportional reporting ratios in order to detect existing signals. Nonetheless, ADRS data quality and utility could be improved through standardisation of objectives and interpretation of national case definitions as was recommended in the Horvath Review.[24]

The two active systems, APSU and PAEDS, provided superior data quality and validity. Firstly, although diagnosis of IS is typically straightforward, both sources—unlike ADRS notifications which could be reported by the general public—relied on reporting by health professionals and subsequent review by expert clinicians. To verify completeness of case ascertainment, PAEDS conducted periodic audits of medical records searching for primary and secondary ICD-coded IS cases and then comparing these with PAEDS data over the same time period. Both APSU and PAEDS used standardised protocols and questionnaires for each condition under surveillance in

order to improve consistency of case reporting.

Data within the fourth surveillance system, hospitalisation inpatient databases, were collected with no intention of reporting on adverse events. However, AIHW performed logical validations on coded data, and coding audits were also performed at the hospital and jurisdictional level.[34] Generally, jurisdictions considered that coding of inpatient data in recent years has been of high quality.[35] Quality may, however, have been limited by variations in recording and coding across jurisdictions and over time. Errors causing the ICD code to differ from the true disease may also have occurred. These may have included both random and systematic measurement errors, potentially stemming from the level of details documented in medical records, clinicians' level of experience or those based on transcribing, and coder errors such as miss-specification.[36] A 2008 Canadian study based on four teaching hospitals demonstrated coding of hospital discharge data sensitivity ranged from 9.3%–83.1% using ICD-9-Canadian Revision and 12.7% –80.8% using ICD-10 codes, depending on the condition reviewed.[37]

For the purposes of IS surveillance, the quality of inpatient data may have been limited by poor completeness of procedure code data. For example, data may not have included whether or not ultrasounds, enemas, or surgery had been administered. Moreover, inpatient data did not collect the outcome of procedures necessary in order to classify cases using Brighton Collaboration criteria. In another limitation, inpatient data did not collect vaccination status, a factor required for risk association studies. However, this non-collection of procedural outcome or vaccination status did not equate to poor data quality per se. But lacking such detail, the inpatient data were limited in usefulness in terms of IS surveillance without conducting chart review or accessing data from the Australian Childhood Immunisation Register (ACIR).

### *Timeliness*

For the purpose of this evaluation, timeliness referred to the interval between an IS case occurrence, its detection, report of it by the relevant surveillance method, and

when the findings based on compiled data were ultimately available for dissemination. Timeliness also referred to the speed of activation of a surveillance system to begin identifying cases.

Timeliness varied widely by source. For APSU, the time from diagnosis to reporting of cases had been estimated in a published evaluation to range from one week to six months.[38] Eighty percent of email cards were noted to have been returned from participating clinicians within one week.[38] APSU cases were classified every three months as confirmed, duplicate, error, etc, with summaries reported in CDI.

When APSU activated emergency surveillance for the H1N1 influenza pandemic, however, reporting largely occurred within ten days and 60% of follow-up questionnaires were returned by fax immediately. Final data for the H1N1 study were published within six months. This demonstrated the potential for APSU to not only be activated quickly as a surveillance method in times of emergency, but also to provide results in a timely manner.

PAEDS data were exported weekly from the hospital sites to the central database. Cases were identified in 'real time' with the only limitations to that being the workload and work schedule of the surveillance nurses. PAEDS, like APSU, demonstrated its ability to be activated quickly and to provide quick data. The system was also used for emergency H1N1 surveillance in 2009.[39, 40] In terms of time between identifying cases and publishing surveillance data, the publication by Buttery *et al* identified IS cases through APSU and PAEDS from 1 July 2007 to 31 December 2008 and submitted these surveillance results for publication in early September 2010.

ADRS had been criticised for possible reporting delays. Though the system has endeavoured to improve data flow by employing TGA contact persons for each jurisdiction, lags in reporting continued. The Horvath Review highlighted this as one area of concern, suggesting simultaneous reporting could occur across jurisdictions with the TGA receiving reports in 'real time' rather than after the fact in batches. Upon receiving notifications, the TGA triaged cases as serious or non-serious, coded them according to MedDRA criteria and entered them into the ADRS database within 48

hours of receipt; in 24 hours in most cases. AEFI data were made available to the public three months after being entered into the ADRS database in the publicly accessible Database of Adverse Event Notifications (DAEN).[41]

Inpatient data were slow to be compiled and made available for researchers. While some hospitals sent data to state/territory health departments within days of discharge, for others it took more than six weeks for records to be completed. Data then had to be transformed into analysable forms, which happened on an approximately six monthly basis (personal communication, October 2013; Dr Lee Taylor, NSW Ministry of Health). Though a hindrance to generating timely analysis, inpatient data allowed access to the greatest number of IS cases. Conversely, active surveillance systems like APSU or PAEDS may have provided quicker immediate data, but the time required to identify sufficient individual cases with which to conduct appropriately powered research may have been substantial. Consequently, for the purposes of IS surveillance, the strength of APSU and PAEDS data from a timeliness perspective was the rapid activation of each system; this ultimately provided rich case data for either limited analyses or for supplementing larger studies reliant on inpatient data.

### *Sensitivity*

Sensitivity referred to the system's ability to positively identify true cases of IS by determining the proportion of true IS cases detected out of all who had the condition. For conditions associated with vaccine safety, sensitivity is a desirable attribute and, because of the magnitude of missing potential cases, is preferential to specificity for signal detection.[42] Note that when conducting risk association studies between vaccines and AEFI, the converse may be true, with specificity potentially of greater importance.

Sensitivity calculations were dependent upon having accurate denominator data. As it was unknown how many IS cases went unreported, estimating sensitivity for each of the individual contributing systems was problematic. Nonetheless, it was possible

without denominator data to compare the number of cases detected by each system over the same time period.

When comparing the systems used to identify IS cases, considerable variation in sensitivity existed. Table 6.5 summarises the number of IS cases detected by the four surveillance systems for the period July 2007–May 2010. All may have been affected by data quality; this may have resulted in cases not having been accurately documented. This was particularly significant for inpatient data, where accurate ICD-coding from medical records was required. The passive ADRS system was known to suffer from under-reporting and bias in reporting of suspected events; this was clearly demonstrated by the comparably smaller number of reports detected (Table 6.5). As demonstrated by Table 6.5, the acute and severe nature of IS meant cases were more likely to be captured more comprehensively via paediatric specialist and hospitalisation data gathered by APSU, PAEDS and in the inpatient databases than by ADRS.

The PAEDS system was a relatively sensitive method for detecting IS—more so than APSU, as not all IS cases were treated by paediatricians involved in APSU data collection. Moreover, because of the severe nature of IS, patients with this condition were more likely to have presented to a hospital in the first instance. In this regard, APSU was perhaps more suited to surveillance of non-acute conditions managed by paediatricians whose patients presented to their consulting rooms.

As demonstrated in Table 6.5, inpatient databases had the ability to capture the largest number of cases: an estimated 31-fold more than ADRS. It should be noted, however, that this included a substantial number of inter-hospital transfers for a single episode. For example, in research involving chart review of NSW ICD-coded cases, 24% of cases were determined to have been duplicates due to hospital transfer.[43] Another notable limitation to inpatient data was the potential for IS cases to present to an ED and not subsequently be included in the inpatient database. This phenomenon was observed at the CHW, where ten IS cases detected by PAEDS were found not to have been included on the inpatient database, as they were managed in the ED without being hospitalised.[43] Similar findings were reported in a 2009 US study.[44]

**Table 6.5. The number of IS cases detected by the four surveillance systems, Australia, July 2007–May 2010**

| System | Number of IS cases |
|---|---|
| ADRS | 44 |
| APSU | 79 |
| PAEDS | 251 |
| National inpatient databases | 1,393* |

*A proportion of these cases will include duplicates due to hospital transfer. Others may not be true cases.[43]

### *Causality ascertainment*

Causality ascertainment required assessment of the 'strength of association, consistency, specificity, biologic plausibility, coherence, experimental evidence and analogy'.[4]

The WHO's report on post-marketing surveillance of rotavirus vaccine safety stated that the 'clearest and most reliable' method for determining whether vaccinations caused adverse events was comparing rates in vaccinated and non-vaccinated groups in randomised clinical trials.[4] When clinical trials were not feasible, observational studies were useful.

Observational studies utilising APSU and PAEDS data were successful in determining an association between vaccination and IS. This was achieved by accessing ACIR data detailing the number of doses of rotavirus vaccine received and the age at vaccination in children with IS. Inpatient data were also able to ascertain causality and estimate vaccination-associated risk associated by accessing additional case information from medical records and vaccination records from ACIR data.

The WHO also affirmed the utility of reviews of serious adverse events to determine the likelihood of them having been caused by vaccination. Accordingly, ADRS surveillance data were useful for IS surveillance. Although reported AEFI may or may not have been caused by vaccination, attempts were made by the TGA to determine causality. Causality was assigned as 'certain', 'probable' or 'possible' based on the

WHO Uppsala Monitoring Centre causality assessment criteria.[30] These rankings assessed the likelihood that the suspected vaccine or vaccines was/were associated with the reported adverse event. Factors contributing to the ranking included 'the timing of the reaction following vaccination, the spatial correlation of symptoms and signs in relation to vaccination and whether one or more vaccines were administered'.[30] A limitation of ADRS's causality assessments was the difficulty in attributing causality; because most infant vaccines were given in combination, determining which vaccine may have caused the suspected AEFI was largely impossible. Consequently, any co-administered vaccines were commonly assigned a causality ranking of 'suspected'.

### *Positive Predictive Value (PPV)*

PPV referred to the proportion of IS cases detected which were true IS cases. For ICD-coded inpatient data, assessing this attribute by reviewing ICD-coded cases of IS using Brighton Collaboration criteria was possible.

NSW inpatient data had previously been chart reviewed and cases assigned Brighton criteria levels.[43] Among NSW cases identified by inpatient data for the period July 2007–June 2010, the PPV of an ICD-code of IS for any diagnosis was 61.5% (Table 6.6). The PPV for primary diagnosis was only slightly improved at 63.1%.

**Table 6.6. Positive predictive value (%) for NSW inpatient data as compared with CHW PAEDS data, July 2007–June 2010**

| Surveillance method | | Number of Brighton Level 1 cases | Total number of ICD-coded cases | PPV (%) |
|---|---|---|---|---|
| NSW inpatient data | | | | |
| | ICD-code of IS for any diagnosis | 110 | 179 | 61.5% |
| | ICD-code of IS for primary diagnosis | 106 | 168 | 63.1% |
| CHW PAEDS data | | 51 | 56 | 91.1% |

In contrast, for CHW PAEDS cases for the period July 2007–June 2010, the PPV was 91.1% (51 cases detected by PAEDS were Brighton Collaboration Level 1 at CHW/56 total PAEDS at CHW). Clearly, PAEDS offered superior precision for detecting true cases.

APSU and ADRS cases were not confirmed using Brighton Collaboration criteria and therefore ascertaining PPV for these systems was not possible.

### *Representativeness*

Representativeness referred to whether or not IS cases identified were representative of cases in the wider population. Inpatient data were thus likely the most representative, although cases presenting to an ED or that were treated as outpatients may have been missed.

Cases detected by APSU only included children <15 years of age (though surveillance for IS was for cases <24 months of age) who presented to paediatricians, other child health specialists in hospitals, private practice or community settings. In 2009, the APSU mailing list of reporting clinicians included approximately 92% of Royal Australian College of Physicians (RACP) Fellows who identified as paediatric specialists or subspecialists in active clinical practice. Though the number of clinicians reporting in

each jurisdiction was proportional to the child populations of each state/territory, APSU has acknowledged that surveillance gaps exist among remote and rural populations.[38]

PAEDS cases were only identified in five tertiary paediatric hospitals and suffered similar surveillance gaps to APSU with regard to remote and rural populations. However, due to the clinical management required, IS cases were frequently transferred to large tertiary paediatric hospitals, many of which were integrated into the PAEDS system. It was estimated in 2011 that the four participating PAEDS hospitals at that time (Royal Children's Hospital Brisbane was included in 2012) were responsible for approximately 70% of all admissions to all seven tertiary paediatric hospitals in Australia.[45] Like APSU, PAEDS IS cases were defined to include only those <24 months of age.

Because ADRS lacked sensitivity, it lacked representativeness despite being a national system accepting notifications from the public as well as health professionals. Lack of awareness about both the system's existence and the methodologies involved in reporting adverse events further compromised its potential representativeness, potentially resulting in substantial reporting bias. Table 6.7 provides an overview of characteristics of reported ADRS IS cases.

Table 6.7. Characteristics of IS cases reported to ADRS, Australia, July 2007–May 2010

| Characteristics of cases reported to ADRS | | | |
|---|---|---|---|
| Age | <1 year | Unknown | |
| | 42/44 (95.5%) | 2/44 (4.5%) | |
| | | | |
| Sex | Male | Female | Unknown |
| | 22/44 (50.0%) | 20/44 (45.5%) | 2/44 (4.5%) |
| | | | |
| Jurisdiction & reporter | State/territory | Total reports | Reports by reporter type |
| | NSW | 19 | Drug company 16<br>State/territory 3 |
| | | | |
| | Queensland | 4 | Hospital 2<br>State/territory 2 |
| | | | |
| | South Australia | 2 | State/territory 2 |
| | | | |
| | Victoria | 13 | Drug company 7<br>Hospital 2<br>State/territory 4 |
| | | | |
| | Western Australia | 6 | State/territory 6 |

## Utility and usefulness

### *Usefulness of individual components*

ADRS data may have been useful for contributing to signal detection and hypothesis generation, and rates were able to be estimated using appropriate denominator data. Data quality, however, was hampered by underreporting, which was compounded by

the rare incidence of IS. Moreover, research using passive surveillance data is typically limited by biases, including that cases reported to passive systems are frequently biased toward those cases identified directly after vaccination.[14] In terms of output, surveillance reports including all AEFI were published in CDI annually. As these reports were national summaries of all AEFI, limited detail was available specifically regarding IS.

Inpatient data were useful for providing large numbers of cases ICD-coded as IS, which assisted in ensuring adequate power for analyses of this rarely occurring condition. Inpatient data were also useful for contributing to analyses of IS incidence both pre- and post- vaccine introduction. Inpatient data, however, were most useful as springboards for research involving detailed chart review to obtain rich clinical data and vaccination status about individual cases.

Active surveillance, however, suffered fewer limitations; with 'verification of diagnoses through review of clinical features and with diagnostic evaluation of potential cases,' it remained the gold standard for identifying cases of IS and was useful for contributing detailed cases for research studies.[14]

As an active surveillance system, APSU was more sensitive than the passive ADRS surveillance at detecting IS. Nevertheless, it was still limited by underreporting and surveillance gaps. PAEDS, in comparison, detected more cases than APSU, was useful in providing rich clinical detail about cases, and provided the opportunity to assess causality. PAEDS utility was further extended as its IS protocol and questionnaire informed the extensive chart review studies that occurred in NSW and nationally. Due to IS's rarity, however, both APSU and PAEDS could be slow to accumulate enough cases to constitute a cohort sizable enough to power observational research studies.

Despite their accumulation of large case numbers, a useful function of both APSU and PAEDS was their ability of rapid activation for emergency surveillance, thereby providing timely data for researchers. Research including APSU and PAEDS data was integral in reporting on the risk associated with rotavirus vaccines, thereby contributing substantially to the international evidence base and informing policy both

nationally and internationally (Table 6.8).

### *Utility of the IS surveillance system as a whole*

In September 2008, at the Public Health Association of Australia's (PHAA's) 11th National Immunisation Conference, APSU data were presented for the first time. APSU had been monitoring the temporal association between rotavirus vaccine receipt and IS since May 2007,[23] and data suggested an association in four out of 37 reported cases who had met the case definition criteria. This alerted Australian health officials to a potentially small risk associated with the two new vaccines, despite large-scale clinical trials declaring no such risk existed.

Including PAEDS data compiled since July 2007 allowed an expansion of this research.[46] All confirmed cases of IS in infants aged <24 months between 1 July 2007 and 31 December 2008 detected by both systems were assessed according to vaccination status (ACIR data) and the time period following vaccination until IS diagnosis. This research suggested an apparent increased risk of IS within one week of receiving the first dose of either vaccine. However, the study also concluded IS rates did not increase over the course of the nine month follow-up of all infants who were vaccinated.

This research prompted the TGA to commission a population-based assessment of risk utilising inpatient data from NSW, Victoria and Western Australia, supplemented by additional cases detected by PAEDS with vaccination history sourced from ACIR data. Researchers conducted a self-controlled case series (SCCS) analysis to assess the level of risk associated with receipt of either vaccine and IS. The study detected an approximate fourfold increase in IS in the first 1–7 days following receipt of the first dose of both Rotarix and RotaTeq[47]—a risk estimate much lower than that associated with the Rotashield vaccine.[48] Subsequently, the TGA issued a statement to healthcare providers informing them of the observed increased risk and stressing their commitment to continuing support of the vaccines due to the widespread benefits of decreasing rotavirus incidence. Contemporaneously with this study, the NSW Ministry of Health commissioned NCIRS to conduct a similar study with chart review to confirm

true cases. This chart review study included a SCCS analysis as well as detailed clinical comparison of cases based on their Brighton criteria levels. A significantly increased IS risk was observed in days 1–7 and 1–21 post-first dose of Rotarix vaccination—the vaccine which NSW administers.[43]

The three state study was expanded to a national investigation for the time period of 1 July 2007 to 31 June 2010 using similar methods and including a SCCS and risk benefit analysis. Results concluded an increased IS incidence in the first 21 days following the first dose of vaccination for both vaccines: a 6–10 fold increase for 1–7 days and a 3–6 fold increase for 8–21 days post-first dose of vaccination. [49] The risk-benefit analysis compared hospitalisations before and after the introduction of the rotavirus vaccine and concluded a slight increase in IS hospitalisations (14 excess cases annually or an excess 5.6 per 100,000 vaccinated children).[49] This TGA-commissioned research ultimately informed changes to the product information for both Rotarix and RotaTeq vaccines; both refer specifically to this Australian study in their product information.[50, 51] Reflecting the updated attributable risk estimates, the TGA's statement to healthcare providers was also re-issued, and parental advice regarding IS risk associated with the vaccines was included on the DOH Immunise Australia website.

This study was the first of its kind internationally to compare IS risk following receipt of both vaccines in similar populations with sizable numbers of cases and over the same time period. The comparison was made possible by the fact that Australian jurisdictions each deliver only one of the vaccines. The results were globally significant for vaccine safety monitoring, and were presented not only to ATAGI but also to the US Advisory Committee on Immunization Practices (ACIP).

Utility of the system—as measured by research output and results which informed both national and international policy—was substantial (Table 6.8).

**Table 6.8. Research output, findings, and impact of four surveillance systems contributing to Australian IS surveillance**

| Surveillance method | Output | Research title | Method of research | Results | Impact |
|---|---|---|---|---|---|
| APSU | Abstract presented at PHAA Conference, September 2008[23] | Preliminary national data on acute intussusception in children aged ≤24 months from the Australian Paediatric Surveillance Unit (APSU) | Initial prospective national case series review of cases reported May 2007–November 2007 alerted a temporal association between rotavirus vaccine and IS | 4 out of 37 reported confirmed cases May 2007–November 2007 | Triggered Government to commission additional research |
| APSU<br><br>PAEDS | Published paper[16] | Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia | All confirmed cases in infants <24 months between 1 July 2007–31 December 2008 reviewed and association with vaccination assessed with ACIR data according to time period following vaccination when diagnosed with IS | An increased risk of IS within 1 week of receiving first dose of either vaccine: RR for IS within 1–7 days of receipt of first dose of 4.48 (95%CI: 0.92–13.09) for RotaTeq and 3.41 (95%CI: 0.70–9.96) for Rotarix | First publication worldwide to highlight association between RotaTeq and Rotarix and IS;<br>Prompted further research to be commission by the TGA |

| Surveillance method | Output | Research title | Method of research | Results | Impact |
|---|---|---|---|---|---|
| Inpatient data | Government report[47] | Rotavirus vaccination and risk of intussusception: a case-series analysis in three states of Australia, July 2007–December 2009 | SCCS analysis using inpatient data (infants <12 months of age) from NSW, Victoria and Western Australia; vaccination status from ACIR | 4-fold increase in IS in first 1–7 days following first dose of either vaccine. For those receiving RotaTeq an increased likelihood of IS occurring for up to 3 weeks after vaccination; 1–2 excess cases of IS per 100,000 infants vaccinated or 4–5 extra cases a year | Informed changes to product information for both vaccines; TGA issues statement to healthcare providers regarding safety of rotavirus vaccines |
| Inpatient data<br><br>PAEDS | Report to NSW Ministry of Health[52]<br><br>Presented at Australian CDC* Conference, 2011[53, 54]<br><br>Submitted for publication 2013[43] | Intussusception in Australia: population-based risk following monovalent human rotavirus vaccine | NCIRS commissioned by NSW Ministry of Health. Chart review based study including case control and SCCS analysis for infants aged <12 months, July 2007–June 2010. Included clinical comparison of cases based on Brighton criteria levels<br><br>Publication did not include case control analysis | SCCS analysis showed increased relative incidence of IS in days 1–7 following first dose of Rotarix [RI†: 11.1 (95% CI: 2.6–48.0)]. IS episodes that were potentially vaccine attributable did not differ in severity from IS occurring outside risk periods | Contributed first Australian clinical assessment of vaccine associated IS hospitalisations according to Brighton criteria level<br><br>Compared risk estimates obtained from Brighton Level 1 confirmed cases with those obtained from all ICD-coded cases |

*CDC: Communicable Disease Control (Conference); †RI: Relative Incidence

| Surveillance method | Output | Research title | Method of research | Results | Impact |
|---|---|---|---|---|---|
| Inpatient data<br><br>PAEDS | Published paper[49]<br><br>Presented to US ACIP[55] | Increased risk of intussusception associated with both currently licensed rotavirus vaccines in Australia's National Immunization Program | From July 2007–June 2010, infants aged <12 months. SCCS analysis using inpatient data (infants <12 months) from NSW, Victoria, Northern Territory, Queensland, South Australia and Western Australia; vaccination status from ACIR | A 6–10-fold increase in risk for days 1–7 after first dose vaccination and 3–6-fold increased risk for days 8–21 after first dose vaccination<br><br>Attributable risk for both vaccines of 5.6 additional cases of IS per 100,000 vaccinated infants or an estimated excess of 14.3 cases annually at the national level | First internationally to compare risk following receipt of both vaccines<br><br>Prompted TGA safety update[56]<br><br>Prompted update by Department of Health and Ageing for parents<br><br>Prompted updating 10th edition Australian Immunisation Handbook[57] |
| Inpatient data | Presented to ATAGI[58] | Risk of intussusceptions and trends in hospitalisations before and after rotavirus vaccination program in Australia | Serial cross-sectional analysis of age-specific IS hospitalisation rates before (July 1998–June 2007) and after (July 2007–June 2010) vaccine introduction; risk-benefit analysis comparing vaccine attributable IS risk with benefits of vaccination; clinical case review, SCCS analysis cohort N5W children (July 2007–June 2010) | An RI of IS (8.4; 95%CI: 2.0–35.7) in 1–7 days after first dose of vaccine. Risk-benefit analysis determined that vaccination program would avert 1,547 cases of all-cause gastroenteritis hospitalisations per year among children <5 years of age in NSW | Contributed historical data to Australian IS epidemiological profile |

Finally, an assessment of the utility of the surveillance system must include consideration of whether its objectives were met. Though objectives of IS surveillance were undefined, objectives were identified based on criteria outlined by the WHO.[4] Table 6.9 details these objectives and how they were achieved.

**Table 6.9. Assessment of objectives of the IS surveillance**

| Objective | Was the objective met? | | Which components contributed |
|---|---|---|---|
| Detecting all suspected cases of IS | Unknown | Cannot be sure that all cases were detected; however, given the seriousness of IS and that cases primarily occur in infants, it is likely that most cases were identified. | All<br><br>Inpatient data particularly important to ensuring all detected |
| Identifying cases for which a causal link can be identified with receipt of either vaccine | Yes (not for all cases) | Three significant studies included chart review which allowed cases' vaccination history to be obtained. | Inpatient data<br>PAEDS<br><br>ACIR data supplemented |
| Compiling thorough and useful case data to contribute to the national descriptive epidemiological profile of IS | Yes | All surveillance systems provided useful data to assist in better understanding IS in Australia. | All |
| Compiling thorough and useful case data to inform incidence and risk analyses | Yes | Five studies were able to conclude estimates of each. | Inpatient data<br>PAEDS<br>APSU<br><br>ACIR data supplemented |

## INTERNATIONAL RELEVANCE

The US CDC's rotavirus vaccine safety website states that many of its studies have been unable to rule out a risk as low as that reported in Australia and elsewhere.[59] Moreover, Australia provided some of the earliest international results regarding the small but significant risk that was unable to be detected in large post-licensure clinical trials. Data from Australia have been particularly important because the country administers both vaccines and has been able to contribute data regarding the safety of both.

Other countries have provided evidence for there being an IS risk associated with receipt of the two rotavirus vaccines. Data from the US Vaccine Safety Database (VSD) have been used to demonstrate a potential one case of IS per 20,000 fully vaccinated infants who received Rotarix. The US Food and Drug Administration (FDA) has published a study estimating a possible 11.5 additional cases of IS per 100,000 US infants within the first 21 days following receipt of the first dose of RotaTeq. Increased risks have been demonstrated in Mexico and Brazil: in Mexico, in the first week following the first dose of Rotarix and in Brazil in the first week following the second dose of Rotarix. These studies, with the data from Australia's studies, led the CDC to conclude that there may be 13 excess cases of IS per 100,000 infants

Further international studies are required to better understand the regional and demographic variability of IS risk associated with rotavirus vaccine receipt. Moreover, since many vaccine products are now 'primarily licensed in, or developed for, exclusive use in low- and middle-income countries'[60], post-licensure safety surveillance efforts in these countries are particularly important (although the financial and infrastructural challenges to do so should not be underestimated). Indeed, the WHO Global Advisory Committee on Vaccine Safety has recommended a standardised approach for vaccine safety monitoring in all countries administering rotavirus vaccines and for all countries intending to introduce the vaccines.[61] A standardised approach will allow for easily understood and comparable data.

Some level of passive surveillance has already been established in many lower and middle income countries.[60] However, due to the limited efficacy of passive surveillance data, countries with limited resources may be better off establishing a network of hospitals—or even a single hospital if funds extend no further—with functioning healthcare databases that could be accessed retrospectively for review. This would require existing databases to contain enough data with sufficient detail to be useful for such analysis. Such a system would allow for some degree of base estimates and for the epidemiological profile of IS cases to be ascertained. As a second step, these same hospitals could consider implementing a type of active surveillance similar to PAEDS with several individuals tasked with detecting cases. Without such hospital-based activities, countries employing solely passive surveillance will have limited abilities to analyse and interpret vaccine safety associated risks.

## RECOMMENDATIONS

While Australian IS surveillance was effective, useful and influential, its success was based on its optimisation of four existing surveillance systems. As future efforts to monitor vaccine safety may well rely upon multiple surveillance methods, ensuring such efforts are coordinated and planned from the outset will be critical, with clear objectives and desired output as well as delegated management roles. Additional recommendations are outlined below.

### Recommendation 1:

Future efforts at post-licensure vaccine safety surveillance should be clearly planned and managed, with objectives articulated from the start. To this end, establishing a Post-licensure Vaccine Safety Surveillance Working Group may be beneficial. The Group could be called upon when needed to outline surveillance objectives, management, resources required, type of research studies necessary, timeline, and

desired output. Moreover, coordination of research studies commissioned by the Government should be clear, with clear delineation of responsibilities.

## Recommendation 2:

In line with Horvath Review recommendations, and in order to maximise the usefulness of the surveillance system, this evaluation stresses the need for harmonised passive surveillance system reporting and information flows across jurisdictions. Passive surveillance for rare AEFI can be important for detecting signals and improving the system would be beneficial. For example, one standardised AEFI reporting form to be used by all states and territories could improve consistency of data collected and reported to ADRS.

## Recommendation 3:

Though funding-dependent, expansion of the PAEDS network to include all states and territories, particularly the Northern Territory if a suitable paediatric facility could be adapted for PAEDS purposes, would maximise the PAEDS system's efficacy and consequently its usefulness for vaccine safety monitoring.

## Recommendation 4:

It would be beneficial for strengthening vaccine safety monitoring if ACIR data included all life-time vaccinations received and not only those received through the age of seven years. This would allow for more comprehensive monitoring of vaccine safety.

## Recommendation 5:

Although data linkage may be challenging, doing so would benefit vaccine safety surveillance immensely. One example, as suggested by a stakeholder, would be linking

ACIR and inpatient data. Another stakeholder suggestion was that reporting cases 'real time' to the TGA through electronic-based ED and inpatient data systems would ensure all PAEDS and APSU cases could be reported to the TGA in 'real time'. This same stakeholder concluded that Australia needs 'an active surveillance system for AEFI that is national, prospective, and timely. Ideally this system should be coordinated by a commonwealth agency such as [the] TGA'.

**Recommendation 6:**

This evaluation would be enhanced by future research involving a capture-recapture analysis to provide an estimate of total IS cases by comparing the proportion of IS cases detected by each surveillance method to the proportion of overlapping cases detected by multiple methods.

## CONCLUSION

Post-licensure vaccine safety surveillance is vital to maintain public confidence in vaccines, particularly so with rotavirus vaccines because of RotaShield's problematic introduction and subsequent withdrawal from the US market. Australia's novel approach to IS surveillance, utilising multiple surveillance methods, has proved successful. Not only has this increased public confidence in the vaccines, it has demonstrated that a combinatorial approach may offer maximal effectiveness. This experience may assist future efforts within Australia to conduct vaccine safety surveillance.

This evaluation also demonstrates the strengths and limitations of individual contributing surveillance methods. These details may assist countries with limited resources to better understand how to maximise existing surveillance resources or which additional surveillance methods would be the most beneficial to improving

vaccine safety surveillance if funding exists.

Moreover, with respect to low- and middle-income countries, high levels of confidence in rotavirus vaccines are of particular importance. It is in these countries where rotavirus-associated morbidity and mortality levels remain high. Since vaccination has proved extremely successful at decreasing rotavirus incidence, the WHO continues to recommend the vaccines remain available despite the small vaccine-related IS risk. However, because of their relatively high expense, low- and middle- income countries often rely on funding assistance to supply rotavirus vaccines; without robust vaccine confidence, such assistance may not be forthcoming.

# REFERENCES

1. Centers for Disease C, Prevention. Intussusception among recipients of rotavirus vaccine-United States, 1998-1999. MMWR - Morbidity & Mortality Weekly Report. 1999;48(27):577-81.

2. Centers for Disease Control and Prevention. Framework for evaluating public health surveillance systems for early detection of outbreaks. MMWR. 2004;53(RR5):1-13.

3. Centers for Disease Control and Prevention. Updated guidelines for evaluating public health surveilllance systems. MMWR. 2001;55(RR13):1-35.

4. World Health Organization. Post-marketing surveillance of rotavirus vaccine safety. Geneva: WHO2009.

5. Newall AT, MacIntyre R, Wang H, Hull B, Macartney K. Burden of severe rotavirus disease in Australia. J Paediatr Child Health. 2006;42(9):521-7.

6. Yen C, Tate JE, Patel MM, Cortese MM, Lopman B, Fleming J, et al. Rotavirus vaccines: update on global impact and future priorities. Hum Vaccin. 2011 Dec;7(12):1282-90.

7. World Health Organization (WHO), cartographer Rotavirus mortality in children younger than 5 years, 2008. Geneva: World Health Organization (WHO); 2012.

8. Galati JC, Harsley S, Richmond P, Carlin JB. The burden of rotavirus-related illness among young children on the Australian health care system. Australian & New Zealand Journal of Public Health. 2006;30(5):416-21.

9. Macartney KK, Porwal M, Dalton D, Cripps T, Maldigri T, Isaacs D, et al. Decline in rotavirus hospitalisations following introduction of Australia's national rotavirus immunisation programme. J Paediatr Child Health. 2011;47(5):266-70.

10. Munos M, Fischer Walker C, Black R. The effect of rotavirus vaccine on diarrhoea mortality. International Journal of Epidemiology. 2010;39:i56-i62.

11. Justice F, Carlin J, Bines J. Changing epidemiology of intussusception in Australia. J Paediatr Child Health. 2005 Sep-Oct;41(9-10):475-8.

12. Bines JE, Kohl KS, Forster J, Zanardi LR, Davis RL, Hansen J, et al. Acute

intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004 Jan 26;22(5-6):569-74.

13. Centers for Disease Control and Prevention. Rotavirus vaccine (RotaShield) and intussusception. [Internet] 2010 [cited 2013 April 8]; Available from: http://www.cdc.gov/vaccines/vpd-vac/rotavirus/vac-rotashield-historical.htm#intussusception.

14. Bines JE, Patel M, Parashar U. Assessment of postlicensure safety of rotavirus vaccines, with emphasis on intussusception. J Infect Dis. 2009 Nov 1;200 Suppl 1:S282-90.

15. Bines J, Ivanoff B. Acute intussusception in infants and children: a global perspective. Geneva: World Health Organization2002.

16. Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, Elliott EJ, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine. 2011;29(16):3061-6.

17. Glass R, Parashar U, Bresee J, Turcios R, Fischer T, Widdowson M, et al. Rotavirus vaccines: current prospects and future challenges. Lancet. 2006;368:323-32.

18. Zanardi L, Haber P, Mootrey G, Niu M, Wharton M, the VAERS Working Group. Intussusception among recipients of rotavirus vaccine: reports to the Vaccine Adverse Event Reporting System. Pediatrics. 2001;107(6):1-6.

19. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. [erratum appears in N Engl J Med 2001 May 17;344(20):1564]. New England Journal of Medicine. 2001;344(8):564-72.

20. Offit P. Rotavirus vaccines: round two. Human Vaccines. [Commentary]. 2006;2(2):84-5.

21. Therapeutic Goods Administration (TGA) DoHaA. Statement on rotavirus vaccines. [Internet] Canberra 2010 [updated 2011; cited 2013 May 7]; Available from: http://www.tga.gov.au/safety/alerts-medicine-rotavirus-100324.htm.

22. World Health Organization. Age of administration of rotavirus vaccines. Geneva:

World Health Organization; 2009 [cited 2014 January 30]; Available from: http://www.who.int/vaccine_safety/committee/topics/rotavirus/rotarix_and_rotateq/7Aug_2009_age_administration/en/index.html.

23. Lloyd-Johnsen C, Bines J, Zurynski Y, Elliott E, Booy R, Richmond P, et al. Preliminary national data on acute intussusception in children aged ≤24 months from the Australian Paediatric Surveillance Unit (APSU). 11th National Immunisation Conference, Public Health Association of Australia; 16-18 September 2008; Gold Coast, Australia 2008.

24. Horvath J. Review of the management of adverse events associated with Panvax and Fluvax. Canberra: Commonwealth of Australia 2011.

25. Department of Health TGA. About the TGA: committees. [Internet] 2012 [cited 2013 October 22]; Available from: http://www.tga.gov.au/about/committees-expert.htm.

26. Department of Health IAP. Immunisation advisory bodies: Australian Technical Advisory Group on Immunisation (ATAGI). [Internet] 2013 [cited 2013 October 22]; Available from: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/advisory-bodies.

27. World Health Organization. Causality assessment of an adverse event following immunisation (AEFI): user manual for the revised WHO classification. Geneva: WHO 2013.

28. Brighton Collaboration. Available definitions. [Internet] [cited 2013 October 23]; Available from: https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions/available-definitions.html.

29. Brighton Collaboration. Who we are. [Internet] [cited 2013 October 22]; Available from: https://brightoncollaboration.org/public/who-we-are.html.

30. Mahajan D, Cook J, McIntyre P, Macartney K, Menzies R. Annual report: surveillance of adverse events following immunisation in Australia, 2010. Commun Dis Intell. 2011;35(4):263-80.

31. The Australian Paediatric Surveillance Unit. About the APSU. [Internet] 2013 [cited 2013 October 22]; Available from: http://www.apsu.org.au/about.

32. The Australian Paediatric Surveillance Unit. Paediatric Active Enhanced Disease Surveillance. [Internet] 2013 [cited 2013 October 22]; Available from: http://www.apsu.org.au/surveillance-systems/paeds/.

33. Australian Institute of Health and Welfare (AIHW). About AIHW. [Internet] 2013 [cited 2013 October 22]; Available from: http://aihw.gov.au/about/.

34. Chiu C, Dey A, Wang H, Menzies R, Deeks S, Mahajan D, et al. Vaccine Preventable Diseases in Australia, 2005 to 2007. Commun Dis Intell. 2010;34(Supplement).

35. Australian Institute of Health and Welfare (AIHW). Australian Institute of Health and Welfare: Australian hospital statistics 2006-2007. Canberra2008.

36. O'Malley KJ, Cook KF, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD codes accuracy. Health Serv Res. 2005;40(5 Pt 2):1620-39.

37. Quan H, Li B, Saunders LD, Parsons GA, Nilsson CI, Alibhaj A, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res. 2008;43(4):1424-41.

38. He S, Zurynski Y, Elliott E. Evaluation of a national resource to identify and study rare diseases: The Australian Paediatric Surveillance Unit. J Paediatr Child Health. 2009;45:498-504.

39. The Australian Paediatric Surveillance Unit. Past studies. [Internet] 2013 [cited 2013 October 22]; Available from: http://www.apsu.org.au/studies/past/.

40. The Australian Paediatric Surveillance Unit. Past PAEDS conditions under surveillance. [Internet] 2013 [cited 2013 October 22]; Available from: http://www.apsu.org.au/surveillance-systems/paeds/past-paeds-conditions-under-surveillance/.

41. Therapeutic Goods Administration. Database of Adverse Event Notifications (DAEN). [Internet] 2013 [cited 2013 October 22]; Available from: http://www.tga.gov.au/safety/daen.htm.

42. Centers for Disease Control and Prevention. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS) -- United States, 1991-2001. MMWR. 2003;51(ss01):1-24.

43. Quinn H, Wood N, Cannings K, Dey A, Wang H, Menzies R, et al. Intussusception in Australia: population-based risk following monovalent human rotavirus vaccine.

Pediatric Infectious Disease Journal. 2013; IN PRESS.

44. Cortese MM, Staat MA, Weinberg GA, Edwards K, Rice MA, Szilagyi PG, et al. Underestimates of intussusception rates among US infants based on inpatient discharge data: implications for monitoring the safety of rotavirus vaccines. J Infect Dis. [19817607]. 2009;200 Suppl 1:S264-S70.

45. Zurynski Y, McIntyre P, Booy R, Elliott E. Paediatric Active Enhanced Disease Surveillance (PAEDS): a new surveillance system for Australia. J Paediatr Child Health. 2013;49(7):588-94.

46. Buttery J, Danchin M, Lee K, Carlin J, McIntyre P, Elliott E, et al., editors. Intussusception following rotavirus vaccine administration: post-marketing surveillance of Rotateq and Rotarix in the National Immunisation Program in Australia [poster presentation]. 28th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID); 2010/05/04/.

47. Carlin J, Lee K. Rotavirus vaccination and risk of intussusception: a case-series and a case-control analysis of confirmed cases from six states and territories of Australia, July 2007 – June 2010. Confidential report to the Therapeutic Goods Administration. Final report. 24 April 2012.

48. Centers for Disease C, Prevention. Withdrawal of rotavirus vaccine recommendation. MMWR - Morbidity & Mortality Weekly Report. 1999;48(43):1007.

49. Carlin JB, Macartney K, Lee KJ, Quinn H, Buttery J, Lopert R, et al. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. Clin Infect Dis. 2013;57(10):1427-34.

50. GlaxoSmithKline. Rotarix © Product Information. 2013.

51. Merck, Co I. Rotateq © Product Information. 2013.

52. Macartney K, Wood N, Cannings K, Quinn H, Wang H, Dey A, et al. NCIRS report to NSW Health on intussusception among NSW infants given Rotarix vaccine2011.

53. Quinn H. Intussusception among New South Wales infants given Rotarix vaccine. Communicable Disease Control Conference; 4-6 April; Canberra 2011.

54. Cannings K. Intussusception and rotavirus vaccination in NSW: clinical review. Communicable Disease Control Conference; 4-6 April; Canberra 2011.

55. Department of Health and Human Services, Centers for Disease Control and

Prevention (CDC). Summary Report. Meeting of the Advisory Committee on the Immunization Practices (ACIP), Jun 19-20; Atlanta 2013.

56. Therapeutic Goods Administration. Rotavirus vaccination and risk of intussusception: A report of TGA's investigation of a possible safety signal. 2011; Available from: www.tga.gov.au/safety/alerts-medicine-rotavirus-110225.htm.

57. Australian Technical Advisory Group on IA. The Australian Immunisation Handbook. 10th ed. Canberra: Australian Government Department of Health and Ageing; 2013.

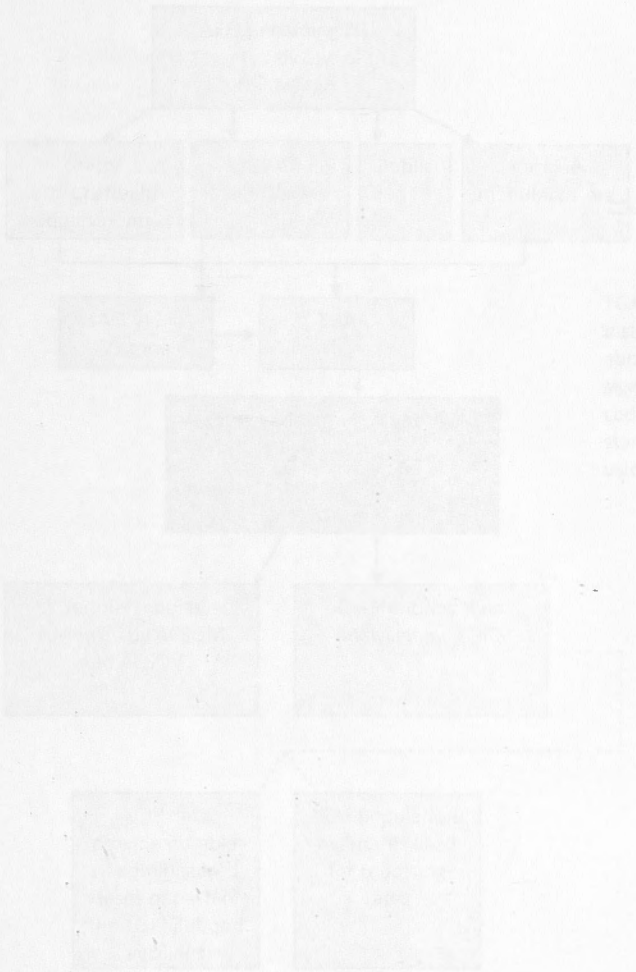
58. Australian Technical Advisory Group on Immunisation (ATAGI). 44th Meeting. February 24-25; Canberra 2011.

59. Centers for Disease Control and Prevention. Rotavirus. [Internet] 2013 [cited 2013 October 22]; Available from: http://www.cdc.gov/vaccinesafety/vaccines/rotavsb.html.

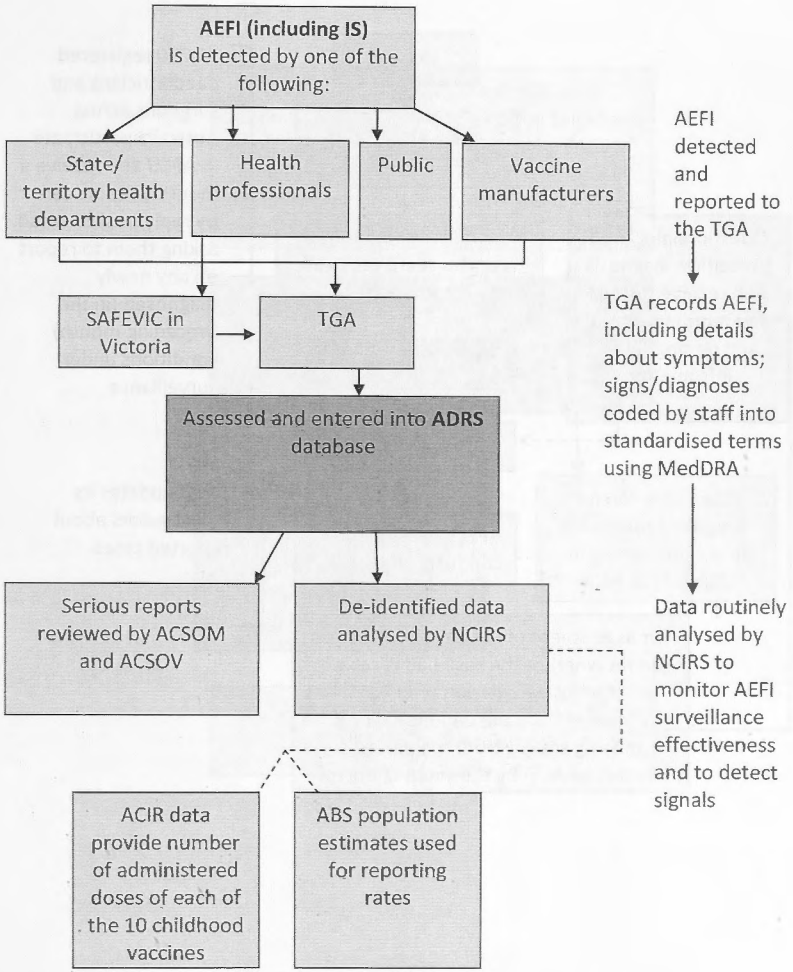
60. World Health Organization. Global vaccine safety blueprint: the landscape analysis. Geneva2012.

61. World Health Organization. Global Advisory Committee on Vaccine Safety, 12-13 June 2007. Weekly Epidemiological Record. 2007;82(28/29):245-60.

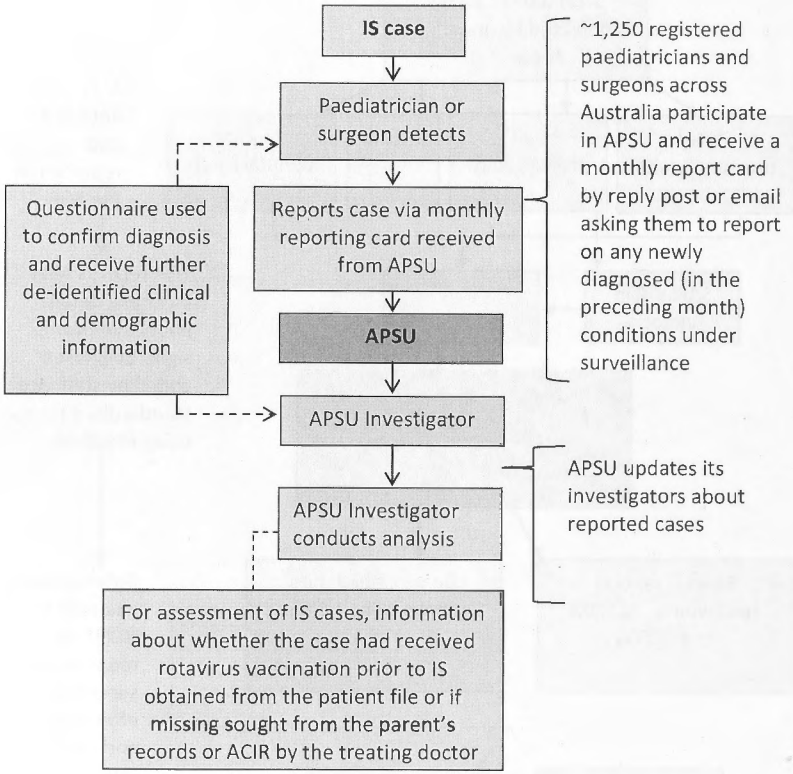
# APPENDICES



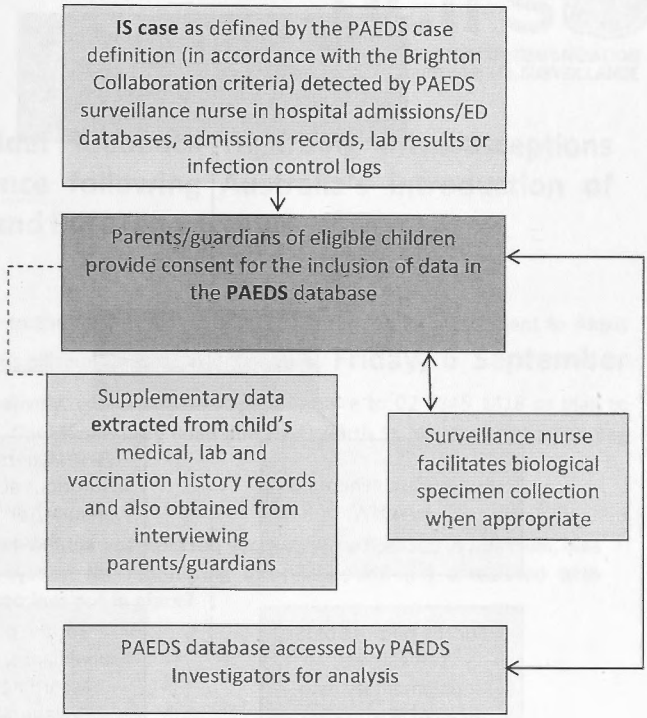
## Appendix 6.A. Overview of how a case of IS is detected and reported by ADRS surveillance



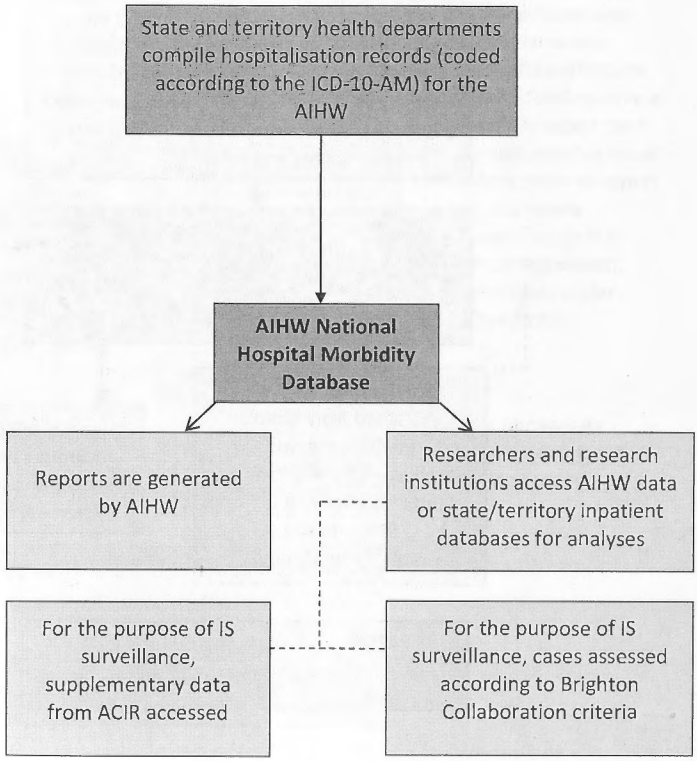
## Appendix 6.B. Overview of how a case of IS is detected and reported by APSU surveillance



## Appendix 6.C. Overview of how an IS case is detected and reported by PAEDS surveillance



## Appendix 6.D. Overview of how hospitalisation inpatient data are used for IS surveillance



## Appendix 6.E. Stakeholder questionnaire used for evaluation


# Stakeholder feedback regarding intussusceptions surveillance following Australia's introduction of Rotarix and RotaTeq vaccines

Please respond to the following questions and return as an attachment to Alexis Pillsbury at alexis.pillsbury@health.nsw.gov.au by **Friday, 6 September 2013.** Alternatively, you can fax the questionnaire to 02 9845 1418 or mail to Alexis at NCIRS, Cnr Hawkesbury Road and Hainsworth St, Westmead, Locked Bag 4001, Westmead NSW 2145.

**1. At the time the Rotarix and RotaTeq vaccines were licensed in Australia, was a surveillance system for monitoring intussusception (IS) associated with receipt of the vaccines put in place?**

☐ No

☐ Yes

☐ Unsure

➢ **If yes, what were the objectives of the surveillance system?**

What did the surveillance system consist of?

Who was in charge of the surveillance system?

- If there was no clear person or group in charge of the system, did this present challenges and if so what were they?

**2. If IS surveillance did occur, was it, in your opinion, successful?**

☐ Not at all successful

☐ Of limited success

☐ Very successful

☐ Unsure

- **If you believe it was successful, what factors contributed to its success? What outcomes demonstrated its success?**

- **If it was not successful, or if its success was limited, what do you think were its main limitations?**

**3. What would be your recommendations for improving future surveillance for adverse events following immunisation?**

**4. Would you like to comment on any other aspect of Australia's rotavirus-IS surveillance? Would you like to comment on any aspects of surveillance for adverse events following immunisation more broadly?**

## Appendix 6.F. Presentation delivered at the 7th Bi-regional TEPHINET Scientific Conference, Danang, Vietnam, November 2013*

Australian National University

ncirs

**Re-thinking traditional adverse event following immunisation (AEFI) surveillance:**

Australia's successful experience of intussusception (IS) surveillance following the 2007 introduction of rotavirus vaccines

Alexis Pillsbury
Master of Philosophy (Applied Epidemiology) Scholar
Australian National University (ANU)
National Centre for Immunisation Research & Surveillance (NCIRS)

### Objectives of presentation

- To provide **background information—intussusception (IS)** & **rotavirus vaccines**
- To explain why Australia required **novel IS surveillance** which used **multiple mechanisms**
- To demonstrate that Australian **IS surveillance** was **successful**
- To summarise **lessons learned** from Australia's experience

Australian National University ncirs

### Intussusception

- Piece of small or large intestine telescopes in on itself
- Early diagnosis & non-surgical reduction reduced morbidity & mortality
- Mortality high in developing countries
- Highest incidence rates in Asia Pacific
  - -Differential/lack of reporting
  - -Regional differences?

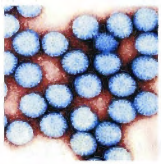
➢ **Underlying cause in infants unknown**

Australian National University ncirs

### Rotavirus

- Commonest cause of gastroenteritis children <5 years
- ~500,000 deaths annually
- Vaccine-preventable

➢ **No known association between IS & rotavirus infection**



Australian National University ncirs

### Link between IS & rotavirus?

September 1998, US


>30 times increased risk of IS

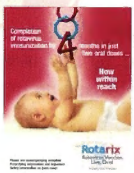
1 excess case per 5,000-10,000 children vaccinated

15 reports of IS (compared with 4 in previous 7 years)

July 1999
**WITHDRAWN**

Australian National University ncirs

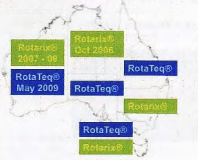
### Mid-2000s: 2 new rotavirus vaccines registered




➢ **Neither** Rotarix nor RotaTeq demonstrated increased IS risk in clinical trials

Australian National University ncirs

## Australia funds both vaccines in National Immunisation Program




- What capabilities existed to detect changes in IS incidence?
- How did IS surveillance evolve?
- Was it successful?




## Methods of evaluation

- WHO & CDC frameworks
- Describe system as a whole
- Assess individual components
- Evaluate success of system as a whole



## Australian AEFI surveillance prior to rotavirus vaccines

- **Passive reporting** of AEFI for previous vaccines
  - Therapeutic Goods Administration (TGA)

- Under-reporting
- No 'control group'
- Multiple vaccines given

➡ **Cannot provide a measure of risk**



## Need for specific IS surveillance

- **Key vaccine experts** identified surveillance need
- Vaccine program **funding did not provide** for IS surveillance
- **Informal system evolved—no overarching coordination or management**
- Utilised **3 additional surveillance mechanisms:**
  - Australian Paediatric Surveillance Unit (APSU)
  - Paediatric Active Enhanced Disease Surveillance (PAEDS)

  } **Surveillance systems**

  - Hospitalisation data

  } **Additional mechanism**



## APSU & PAEDS surveillance systems

| | APSU | PAEDS |
|---|---|---|
| SYSTEM: | APSU | PAEDS |
| ESTABLISHED: | 1993 (IS 2007) | 2007 |
| COVERAGE: | National | 5 paediatric tertiary hospitals |
| AGE: | <15 years (IS: <24 months) | <15 years (IS: <24 months) |
| CONDITION: | Rare, serious childhood conditions | Rare, vaccine-related childhood conditions |
| REPORTER: | ~1300 paediatricians | Surveillance nurses |



## APSU & PAEDS surveillance systems

| | APSU | PAEDS |
|---|---|---|
| National coverage | ✓ | X |
| Active | X | ✓ |
| *Appropriate population targeted* | ✓ | ✓ |
| Appropriate setting targeted | ✓ | ✓✓ |
| Identifies cases real-time | X | ✓ |
| Measure of risk possible | ✓ | ✓ |

## Additional: hospitalisation data

- State/territory & national aggregated data
- All ages: public & private admissions
- ICD-coding—diagnoses & procedures

**Strengths**:
-Historical IS data
-Large numbers of cases
-Link to medical records & vaccination register

**Weaknesses**:
-Validity of coding
-Accessing supplementary data time-consuming

Australian National University ncirs

### IS surveillance achievements, July 2007-May 2010, children aged <2 years

IS cases contribute to annual reporting of national numbers of AEFI

| Mechanism | Number of IS cases identified | Demonstrated risk of IS associated with vaccine | Outputs |
|---|---|---|---|
| TGA | 44 | No | |
| APSU | 79 | Yes | |
| PAEDS | 251 | Yes | |
| Hospitalisation data + chart review | 1393 | Yes | |

Australian National University ncirs

## APSU/PAEDS

First international publication to highlight temporal association between receipt of both vaccines and increased IS cases

Australian National University ncirs

## PAEDS/Hospitalisation data

First epidemiological study internationally presenting risk following receipt of both vaccines in the same country

0.6 excess IS cases per 10,000 vaccinated children

Australian National University ncirs

## PAEDS/Hospitalisation data

Informed changes to product information and safety updates from TGA

Australian National University ncirs

## Lessons learned from Australian IS surveillance

- **Australia 1st in world** to **detect IS risk** associated with new vaccines
- Surveillance using **tailored mechanisms more effective** than routine passive surveillance
- **Hospitalisation data** & **active hospital-based surveillance** beneficial
- Identified key **issues** & **methods** for **case detection** of **relatively rare events**

New vaccine introduction → Pre-emptive safety surveillance plan → Issues specific to new vaccine

Australian National University ncirs

## Importance of improving AEFI surveillance

- Vaccine programs more established in low- & middle-income countries, **vaccine safety monitoring** increasingly **important everywhere**
- Vaccine safety monitoring **aids vaccine confidence**—important for ensuring **vaccines stay available** & **affordable**
- **IS is bad but rotavirus is worse**—
  Vaccine safety monitoring helps ensure we can persist in fight against rotavirus


## Acknowledgements

Dr Helen Quinn
A/Prof Kristine Macartney
Prof Peter McIntyre
Dr Martyn Kirk


Australian National University ncirs

Australian National University ncirs

ncirs
NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

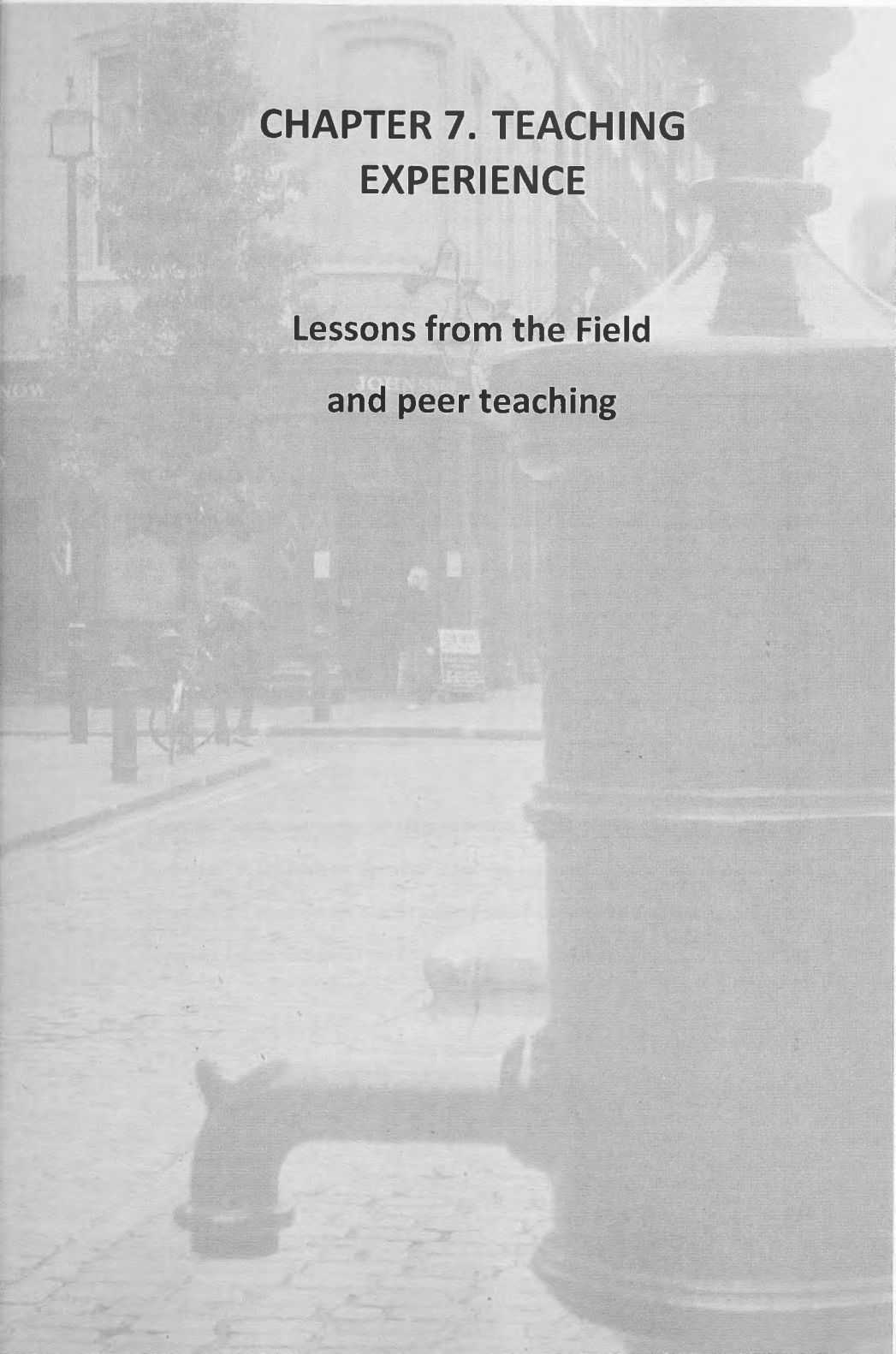
ncirs

*Note: Data included in this presentation may be different from those included in the preceding report due to data having been updated.

# CHAPTER 7. TEACHING EXPERIENCE

## Lessons from the Field

## and peer teaching



# TABLE OF CONTENTS

# PREFACE

## Background and scope of the chapter

In the spirit of learning by doing, a core requirement of the Master of Philosophy Applied Epidemiology (MAE) is teaching experience. This chapter includes materials which I created and taught in various teaching sessions.

Part One of this chapter contains my Lessons from the Field session ('Money matters: a brief introduction to health economic evaluation and cost-effectiveness assessments in publicly funding vaccines in Australia') which I designed and taught to four MAE colleagues via teleconference. Part Two consists of materials for the Epi Info™ 7 training session I taught along with four MAE colleagues at a workshop offered to Communicable Disease Control (CDC) Conference (Canberra, March 2013) attendees on the pre-Conference workshop day. Epi Info™ is a public domain software program created by the US Centres for Disease Control and Prevention (CDC) for global public health practitioners.

## Role and contribution

I planned, developed and taught my Lessons from the Field session. In choosing the topic, I wanted to share with colleagues an area I had exposure to that they possibly did not. As all members of my cohort had clinical and/or scientific backgrounds, I opted to share a more social science oriented topic with them. My undergraduate studies included economics; I also studied health economic evaluation during my Master of International Public Health (MIPH). While by no means an expert in the area of economic evaluation, I was sufficiently confident to create and conduct a teaching session on the basics, with the aim of introducing the broad concepts to my peers. Constructing the session around vaccine funding was an obvious choice given my field placement. The session was created based on content from the National Centre for Immunisation Research and Surveillance (NCIRS) and the US CDC. The Lesson appears

in this chapter and the answer guide is included in the appendices (Appendix 7.A).

The Epi Info™ training session was planned, developed and taught in conjunction with my MAE colleagues Dr Ranil Appuhamy, Ms Rowena Boyd, Ms May Chiew and Dr Ee Laine Tay. We had ten students register for the workshop. Students were public health practitioners from a variety of workplaces and experience levels who were attending the CDC Conference.

Roles varied in the session's planning and management, and each team member was responsible for creating and conducting a portion of the teaching. Because the workshop was taught as a step-by-step introduction to the Epi Info™ 7 software, we all participated as roaming tutors assisting students when we were not specifically teaching. I was responsible for monitoring workshop registrations and ensuring registrants received the necessary logistical information. I created and taught the introductory session of the workshop, which is included in this chapter. The other sections are not included due to the length of the teaching material. However, the schedule for the workshop, the evaluation of the workshop (drafted by Dr Appuhamy) and its results are included as appendices (Appendix 7.B, 7.C and 7.D).

The Epi Info™ 7 workshop was based on similar workshops designed by Drs Stephanie Davis and Kamalini Lokugue of the National Centre for Epidemiology and Population Health (NCEPH) at the Australian National University (ANU). It also incorporated elements of the Epi Info™ 7 Quick Start Guide.[1] The dataset used in this session was obtained from Epi Info™ 7 training materials available from the US CDC.

Finally, as part of my teaching experience requirements, I also assisted in teaching sessions of NCEPH's Outbreak Investigation course to 2013 MAE students and others enrolled in the course. Primarily this involved leading and facilitating small group sessions and providing roaming assistance to students during computer-based sessions.

## Lessons learned

Teaching a workshop about the Epi Info™ software presented particular challenges. Questions asked by students were not easily predictable and on-the-fly troubleshooting in response to questions asked was difficult. Because issues existed with the software program running smoothly for all students on the day, the session was also a good experience in keeping calm and progressing a teaching session despite such problems. Moreover, teaching the session with four colleagues was a solid exercise in collaboration.

Finally, both teaching experiences, as well as the additional experience of assisting with the Outbreak Investigation course sessions, were humble reminders that teachers may not know everything and that admitting that to students is acceptable. These teaching experiences also demonstrated that sometimes it is the teachers who learn from the students.

## Acknowledgements

My Lessons from the Field session proved successful because of the participants: Ms Rowena Boyd, Ms May Chiew, Ms Tove Fitzgerald and Dr Ee Laine Tay. All put great effort into understanding the content and answering questions. I appreciate the time they spent and the positive feedback they offered.

The Epi Info™ 7 training session was a group effort and I appreciate the work my peers did for this workshop. Additionally, Drs Stephanie Davis and Martyn Kirk provided guidance and feedback. Like my Lessons from the Field session, this workshop would not have been successful without the efforts of the participating students. Moreover, it would not have been possible without the CDC Conference allowing us to conduct a Pre-Conference workshop, their organisers assisting us with logistics, and ANU providing a location for the workshop. Additionally, I would like to thank Dr Stephanie Davis for allowing me as part of this MAE requirement to assist in several sessions of her Outbreak Investigation course.

Finally, I would like to acknowledge that the materials used in these various teaching sessions incorporated elements from existing materials. Specifically, I incorporated elements of the US CDC's series on economic evaluation; NCIRS's Vaccines in Public Health workshop; the US CDC's Epi Info™ 7 training materials and Quick Start guide; Epi Info™ 7 training materials created by Harold Collins of the US CDC which appear in the Epi Info™ Community of Users in phConnect[2]; and Drs Davis and Lokugue's (NCEPH) Epi Info™ 7 training workshops.

# ABBREVIATIONS

| | |
|---|---|
| **7vPCV** | 7-valent Pneumococcal Conjugate Vaccine |
| **ACPM** | Advisory Committee on Prescription Medicine |
| **ANU** | The Australian National University |
| **ATAGI** | Australian Technical Advisory Group on Immunisation |
| **CA** | Cost Analysis |
| **CBA** | Cost-Benefit Analysis |
| **CDC** | Communicable Disease Control (Conference) |
| **CDC** | Centers for Disease Control & Prevention (US) |
| **CEA** | Cost-Effectiveness Analysis |
| **CER** | Cost-Effectiveness Ratio |
| **CUA** | Cost-Utility Analysis |
| **DALY** | Disability Adjusted Life Year |
| **DOB** | Date of Birth |
| **IPD** | Invasive Pneumococcal Disease |
| **MAE** | Master of Philosophy Applied Epidemiology |
| **MCCV** | Meningococcal C Vaccine |
| **MIPH** | Master of International Public Health |
| **NCEPH** | National Centre for Epidemiology & Population Health |
| **NIP** | National Immunisation Program |

| | |
|---|---|
| **PBAC** | Pharmaceutical Benefits Advisory Committee |
| **PBS** | Pharmaceutical Benefits Scheme |
| **QALY** | Quality Adjusted Life Year |
| **STEC** | Shiga-Toxin Producing *E. Coli* |
| **TGA** | Therapeutic Goods Administration |
| **WHO** | World Health Organization |

# LIST OF TABLES

# LIST OF FIGURES

# PART ONE

# LESSONS FROM THE FIELD

# Lessons from the Field

# Money Matters:

## A brief introduction to health economic evaluation and cost-effectiveness assessments in publicly funding vaccines in Australia

Alexis Pillsbury

Master of Philosophy Applied Epidemiology (MAE) Scholar

Australian National University (ANU) &

National Centre for Immunisation Research & Surveillance (NCIRS)

13 May 2013

The **learning objectives** for this Lesson From the Field are:

- To introduce the various types of health economic evaluation;
- To learn how to frame a basic health economic evaluation;
- To learn how to approach costing inputs and outcomes for an evaluation;
- To learn how to select and calculate an appropriate summary analysis for an evaluation;
- To understand the various components considered by the Australian Government when deciding whether to publicly fund a vaccine;
- To give a brief overview of the process by which Australia adds a new vaccine to its vaccination schedule.

## Part 1: Case Study Introduction

It is May 2002 and you have recently completed your Master of Applied Epidemiology (MAE) studies and been employed as a research epidemiologist assisting a very important infectious disease professor. The important professor is one of the primary advisors for the Australian Technical Advisory Group on Immunisation (ATAGI). ATAGI provides advice to the Minister of Health regarding Australia's National Immunisation Program (NIP).[3]

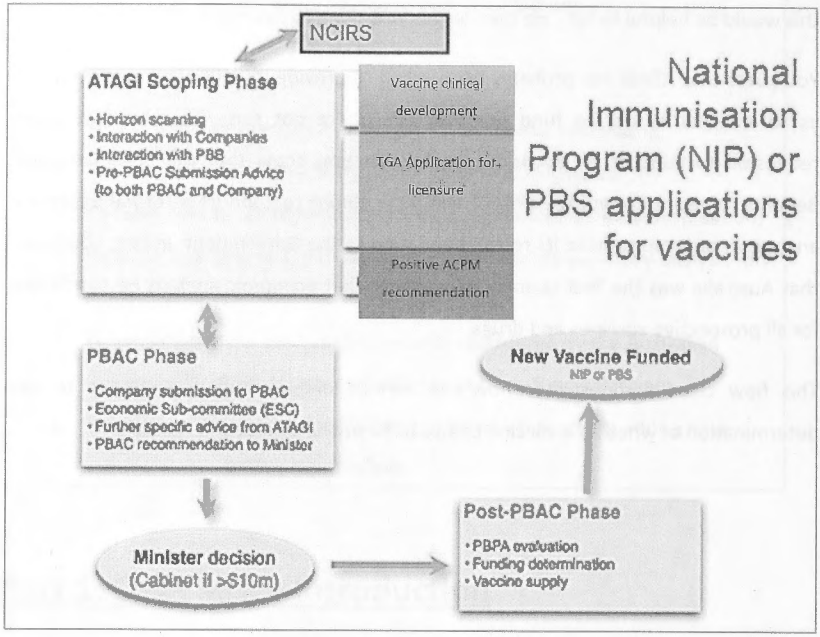
On your first day on the job, your boss asks you to conduct a brief economic analysis considering the costs of publicly funding the newly developed and licensed 7-valent pneumococcal conjugate vaccine (7vPCV) into the childhood National Immunisation Program. The proposed vaccination program would consist of three doses given at 2, 4 and 6 months to the approximate 250,000 <1 year olds in Australia. Since 2001 a program has been funded for all Indigenous and high-risk infants.

Your boss apologises as he knows that this is not your area of expertise but says that this would be helpful to him. He then leaves you alone to figure out what to do.

You guess that ATAGI has probably been asked to provide its official recommendation as to whether or not to fund this vaccine. You're not sure why you have been requested to conduct an economic analysis as you know that the Pharmaceutical Benefits Advisory Committee (PBAC) will be required to conduct a formal economic analysis in order to provide its recommendation to the Government. In fact, you know that Australia was the first country to mandate that economic analysis be conducted for all prospective vaccines and drugs.

This flow chart demonstrates how the various official bodies contribute to the determination of whether a vaccine comes to be publicly funded in Australia:

Figure 7.1. Overview of how a new vaccine becomes funded in Australia[3]




TGA: Therapeutic Goods Administration; ACPM: Advisory Committee on Prescription Medicines; PBS: Pharmaceutical Benefits Scheme

As you cannot argue with your new boss on your first day of work, you decide you'd better learn about health economic evaluations and attempt to deliver him a basic analysis.

First, you find a copy of *Invasive pneumococcal disease in Australia, 2002*[4] on your desk and read:

*"Infection with* Streptococcus pneumoniae *is responsible for significant morbidity and mortality worldwide, especially in the very young, the elderly and those with predisposing risk factors. It is a leading cause of otitis media, pneumonia, bacteraemia, meningitis and a less frequent cause of other conditions including septic arthritis and mastoiditis. Invasive pneumococcal disease (IPD) is defined as a clinical condition in which* S. pneumoniae *infects a normally sterile site, e.g. blood, cerebrospinal fluid or*

*pleural fluid. IPD presents most commonly as pneumonia in adults and bacteraemia in children. The risk of disease is highest among people who are immunocompromised or have a chronic illness. In developed countries, the incidence rate of IPD is bimodal, with a peak in children under 2 years and another peak in adults over 65 years."*

## Part 2: Economic Evaluation Basics[5]

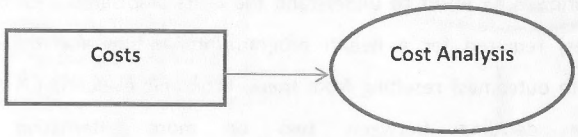
Economic evaluation is an effort to understand the costs associated with both the inputs (resources) required for a health program/intervention and the outputs (changes in health outcomes) resulting from them. Economic evaluation is a critical component for deciding between two or more alternative health programs/interventions.

Conducting a health economic evaluation is, however, not all about adding and subtracting dollars. The exercise requires input from many disciplines, including biology and epidemiology as well as a thorough understanding of the political and social context within which your program/intervention is being proposed and will function.

There are **4 types of economic evaluation**:

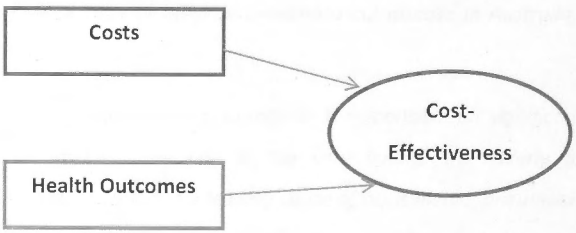
**Cost Analysis**:

Cost analysis (CA) considers the net costs (in dollar terms) of a program/intervention. It is not concerned with costing the outcomes of the program/intervention because the outcomes are either unavailable or they are equally effective between the program/intervention alternatives. A CA often supplements other economic evaluations.



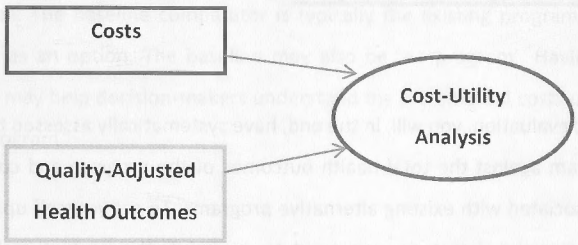

**Cost-Effective Analysis**:

Cost-effective analysis (CEA) compares the costs of alternative programs/interventions that will result in a common health effect which is expressed in natural health units (e.g., a case of disease prevented) rather than in monetary units. A CEA uses a cost per unit of health outcome as its summary measure.



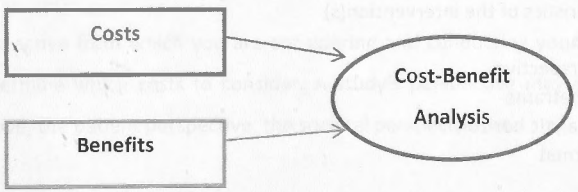
**Cost-Utility Analysis**:

Cost-utility analysis (CUA) is a type of CEA that considers the utility (or a person's preference for a health outcome) associated with different health outcomes. Outcomes are measured in quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs).[6] Cost-utility analysis uses the dollar value per QALY or DALY saved as its summary measure.




**Cost-Benefit Analysis**:

Cost-benefit analysis (CBA) standardises both costs and benefits in dollars and includes all costs and benefits accrued in a time period. CBA uses a single dollar value as its summary measure.



Deciding which type of economic analysis to employ typically depends on whether outcomes need to be assessed and what level of information the decision-makers desire.

**Question 1: Which type of economic evaluation do you think would be the most appropriate for deciding whether to fund the 7vPCV vaccine and why? (2 minutes)**

## Part 3: Framing the Analysis[7]

For an economic evaluation, you will, in the end, have systematically assessed the total costs of a program against the total health outcomes of the program and compared that to costs associated with existing alternative programs. To set yourself up for that final summary measure, however, you need to approach the evaluation like any academic exercise and consider it as a study which you will conduct. Framing is the first step in an economic analysis study and it requires you to outline what you need to know for your evaluation and how you are going to find that information. It should include:

- Study problem
- Problem importance
- Characteristics of the intervention(s)
- Audience
- Study perspective
- Study timeframe
- Study analytic horizon
- Study format
- Costs
- Outcome measures

**Question 2: What is the study problem? (I.e., what is the question you are trying to answer?) (2 minutes)**

**Question 3: Why is this problem important? What aspects of the problem do you need to understand in order to grasp its importance in light of the Government's decision on whether or not to fund the vaccine program? (5 minutes)**

All relevant interventions should be included for comparison in an economic evaluation. The baseline comparator is typically the existing program and should be included as an option. The baseline may also be 'no program'. Having the baseline included may help decision-makers understand the incremental costs of implementing a new program.

**Question 4: What is/are the alternative intervention(s)? What characteristics of the alternatives would be useful for you to understand in order make a comparison with the proposed program? (5 minutes)**

**Question 5: Who is the audience for this study? (I.e., who is interested in or will use the results?) (2 minutes)**

The perspective from which you are considering and conducting your evaluation will help determine which costs to consider. A study's perspective may be the provider perspective, the patient perspective, the societal perspective, etc.

**Question 6: What is the study perspective? (I.e., from whose viewpoint is the study being conducted?) (2 minutes)**

**Question 7: What would be a realistic timeframe for the study? (I.e., what is the period of time during which the program/intervention will be implemented?) (2 minutes)**

**Question 8: What is the study's analytic horizon? (I.e., what is the entire period during which costs and benefits related to the impact of the program/intervention will be measured?) (2 minutes)**

Study formats outline the ways you will collect your data and conduct analyses for the economic evaluation. Options include:

- Prospective study
- Retrospective study
- Model

A prospective study collects outcome and cost data after the study begins. A retrospective study reviews costs and outcomes that have already been incurred. Modelling can be used to create a representation of what you think will happen when you implement the program/intervention.

Table 7.1. Pros and cons of economic evaluation study formats[6]

| | Pros | Cons |
|---|---|---|
| **Prospective study** | More control over data quality | Time- and resource-intensive; possibility for observer bias |
| **Retrospective study** | Time-saving | Less control over quantity and quality of data |
| **Modelling** | Less reliance on direct data; more flexible | Validity of underlying assumptions questionable |

**Question 9: What do you think would be the most appropriate/realistic study format to use for this evaluation? (I.e., how will you assess the program/intervention?) (2 minutes)**

The costs in an economic evaluation can be both tangible and intangible. Tangible costs include direct medical costs (hospitalisation costs, pharmaceutical costs, medical supplies, etc), direct nonmedical costs (program administration, patient travel costs, etc) and productivity losses (time used by patient or caregiver accessing healthcare, wages lost because of accessing healthcare, etc). Intangible costs are emotional ones and are typically not included in an economic evaluation because they are difficult to quantify.

Table 7.2. Costs included in each type of economic evaluation[6]

| | Direct medical costs | Direct nonmedical costs | Productivity losses | Intangible costs |
|---|---|---|---|---|
| CBA | X | X | X | X |
| CUA | X | X | | |
| CEA | X | X | X | |

**Question 10: What costs do you think should be included in the analysis? Include both the type of cost and some specific examples. (5 minutes)**

An outcome measure is a unit used to assess the output of the program/intervention. Outcomes can be measured in monetary units (CBA), quality-adjusted health outcomes (CUA), or natural units (CEA). Choosing which outcome measure depends on what is most appropriate for the study and what data are available.

An outcome measure may be an intermediate outcome or a final outcome. An intermediate outcome is the short/near-term effect of the program/intervention and a final outcome measure is the ultimate or long-term health outcome of interest. Often intermediate outcomes are more realistic to measure because the final outcome data are not available.

**Question 11: What would be the intermediate and final outcome measures in your evaluation? (3 minutes)**

The final summary measure of your evaluation depends on the type of evaluation conducted and the specific outcome you are reporting on.

Table 7.3. Summary measures used for each type of economic evaluation[6]

| Economic evaluation | Summary measure |
|---|---|
| CBA | Net benefits<br>(benefits – costs) |
| CUA | Cost-utility ratio<br>(net costs/QALY) |
| CEA | Cost-effectiveness ratio<br>(net costs/cases prevented) |

**Question 12: What will be the final summary measure in this evaluation? (2 minutes)**

## Part 4: Assessing Costs and Outcomes[8, 9]

Once you have the framing structure for your analysis, the next step is assessing costs and outcomes. For a CEA, all tangible costs are included. The net cost is the cost of the program/intervention minus the cost of disease averted and the cost of productivity losses averted.

**Net cost =**

**Program cost – Cost of disease averted – Cost of productivity losses averted**

Essentially, you are subtracting the overall savings from the total cost of the program. The cost of disease averted and cost of productivity losses averted are subtracted because they are savings. If you excluded them from the equation, you'd be overestimating the costs.

If you are considering the evaluation from a societal perspective, then you will incorporate productivity losses averted. If, however, you are employing a healthcare system or provider perspective, you might not include productivity losses.

Your boss has left you this information provided by consultants who were hired to estimate the costs relevant for this vaccine:

**Table 7.4. Estimated program costs of 7vPCV**[9,10]

| | |
|---|---|
| **Vaccine cost per dose** | $90.00 |
| **Administration fee per dose** | $5.00 |
| **Number of doses required** | 3 |
| **Population of children <1 year of age** | 250,000 |

**Question 13: What are the anticipated program costs based on the estimations in the table above? (2 minutes)**

| |
|---|
| Cost of vaccination:<br><br>Total vaccination cost (for each child x 3 doses) =<br><br>Total administration cost (for each child x 3 doses) = |

You have now estimated the total program costs. In Question 10 you listed medical and nonmedical costs associated with the vaccination program as well as productivity losses. You now need to measure and value these costs.

If you were actually conducting a thorough cost-effectiveness analysis, you would systematically identify each cost one-by-one and then provide a measurement of each cost and a valuation of each cost.

For example, if you were evaluating a program which aimed to conduct neighbourhood fogging/anti-mosquito spraying in Vietnam, you would identify as a cost the yearly wage for the program duration for the X number of local staff. You would then measure that cost by consulting with appropriate experts to determine the number of staff needed (prospective study) or ultimately by the number of contracts signed (retrospective study). To value this cost, you could consult local experts as to the standard salary for this type of program worker, or you could consult the World Health Organization (WHO) which provides data outlining the average yearly wage (and other key statistics) for skilled workers and goods per region.[10] For a retrospective study, you could consult the project accounting records and timesheets.

You should note that all costs are typically discounted 3% annually.

Lucky for you, the consultants have also done a summary of the treatment costs associated with all pneumococcal disease states and sequelae.

Table 7.5. Treatment costs associated with implementing the 7vPCV program[9]

| | |
|---|---|
| **Total treatment costs - with no vaccination program** | $144.2 million |
| **Total treatment costs – with vaccination program** | $127.3 million |

You decide for simplicity sake to ignore non-medical costs and productivity losses for the time being because the consultants did not include that information. More importantly, because you are primarily concerned with conducting the evaluation from the Government's (or funder's) perspective you can skip including the costs of productivity losses.

**Question 14: What is the net cost of implementing this program? (3 minutes)**

Total program costs (from Question 13) =

Total treatment costs - no vaccination program =

Total treatment costs - with vaccination program =

Difference in treatment costs between no vaccination and implementing the vaccination program =

Total costs of implementing this vaccination program =

Net cost = Program costs – disease costs averted* =

(*Averted costs are those which are not incurred as a result of the program being implemented.)

In order to determine your final summary measure, you need a measure of natural health units in order to derive the cost-effectiveness ratio (net costs/cases averted).

Lucky once more, you also have information on the baseline rate of disease with no vaccination program and the anticipated reduction in disease associated with program implementation:

Table 7.6. Pneumococcal disease incidence and mortality rates[10]

| | |
|---|---|
| **Baseline disease with no vaccination program** | 588 cases pneumococcal disease (not including pneumonia and otitis media) |
| **Anticipated number of cases with vaccination program implemented** | 36 cases |
| **Difference** | 552 cases |
| **Baseline deaths with no vaccination program** | 36.6 deaths |
| **Anticipated number of deaths with vaccination program implemented** | 24.2 deaths |
| **Difference** | 12.4 deaths |

So you know that the vaccination program would reduce the burden of disease to 36 cases and 24.2 deaths annually.

**Question 15: How many health outcomes would be prevented by the vaccination program? (2 minutes)**

You now need to calculate the cost-effectiveness ratio (CER) to summarise your results

as a cost per unit of health outcome.

**Cost-effectiveness ratio = net cost/ total health outcomes prevented**

**Question 16: Calculate the CER in terms of cost per case of disease prevented and cost per death averted. Interpret these results – what do they mean? (5 minutes)**

**Question 17: Is this an expensive vaccine program? What is your instinctive opinion (and basic recommendation to your boss) on whether it is cost-effective or not? (5 minutes)**

You summarise your evaluation framework and include your rough calculations from Question 16 for your boss.

You decide that you ought to mention that there are limitations to your results. Specifically, you are aware that while a cost-effectiveness evaluation gives you some figures to work with, a Decision Analysis would take into account the uncertainty in events and outcomes and provide a more detailed consideration of alternatives and probabilities.

Though you don't have time to conduct a proper Decision Analysis, you decide that it would be useful to highlight some sensitivity analyses which could be employed to test a range of probabilities and outcomes.[7] You are very aware that, for example, the cost of vaccine administration may vary so you list what you believe could be the high and low range of possible values for this cost and re-calculate the program costs accordingly.

**Question 18: What other parameters should be subjected to sensitivity analyses? (3 minutes)**

Your boss thanks you for your effort and tells you this is a great help to him to have a better feel for the cost component of the 7vPCV program.

He then tells you that ATAGI is also considering funding the meningococcal C vaccine (MCCV) for infants <12 months of age (1 dose) but that there is only enough money to fund one of the vaccines. He provides you with the following information regarding the MCCV vaccine:

Table 7.7. Estimated costs and outcomes associated with implementing the MCCV program[10]

| | |
|---|---|
| **Net cost of MCCV program** | $9.6 million<br>(Net cost = $10 million program cost - $400,000 treatment costs) |
| **Anticipated decrease in meningococcal cases annually under vaccination program** | 130 |
| **Anticipated decrease in meningococcal deaths annually under vaccination program** | 13 |
| **Cost per case of disease averted under MCCV vaccination program annually** | $73,846 |
| **Cost per death averted under MCCV vaccination program annually** | $738,462 |

**Question 19: Roughly, how does this compare with what you worked out for the cost-effectiveness of the 7vPCV program? What would your recommendations to your boss be in terms of which vaccine to fund? What types of information would help you to better make your recommendation? (8 minutes)**

Not long after you provide your recommendation to your boss, you notice several items in the media regarding pneumococcal and meningococcal diseases:

## A mother, a grandfather, a gym worker and a boy are the latest to die of suspected meningococcal. The toll is now 12

# RANDOM KILLER

Colin Shearer, aged 55

Amanda Paget, aged 18

John Pio, aged 10

By LILLIAN SALEH and RACHEL MORRIS

FOUR more people have died from suspected meningococcal disease, taking the NSW toll to 12.

In this special investigation, *The Daily Telegraph* has uncovered how this is shaping as one of the deadliest years on record, with the virus striking young and old alike.

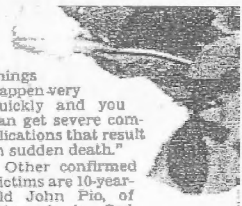
Last week, mother-of-three Jodi Lord was rushed to hospital complaining of severe headaches — hours later she was dead. While the coroner is still investigating the official cause of Mrs Lord's death, traces of meningococcal disease were found in her system.

And yesterday it was also revealed a 33-year-old female city gym employee died on Monday in St Vincent's Hospital.

Australian Medical Association NSW president, Dr Choong-Siew Yong, said the scariest thing about the illness was not knowing what to do about it.

"Scientists don't fully understand why sometimes you get these outbreaks and other times people don't seem to be affected by it," he said.

"When you get an infection, things happen very quickly and you can get severe complications that result in sudden death."



Other confirmed victims are 10-year-old John Pio, of Dharruk in Sydney's west, and 55-year-old Colin Shearer, of Jesmond, in Newcastle. One in eight people who have contracted meningococcal this year

Continued Page 4

Key Video | Q&A Chat | Transcripts | Vote

## Counting the cost

**August 18, 2002**

Reporter: Tara Brown. Producer: Stephen Taylor, Lincoln Howes.

The deadly meningococcal disease.

Watch Video

28k-56k or 100k-300k

Should the federal government commit funds to the fight against meningococcal disease?

- Yes
- No

The very words "meningococcal disease" prompt fear. The first sign of a symptom causes panic. It's a terrifying disease that can maim and kill in hours.

Babies and young adults are most at risk and right now is the peak danger period. To make matters worse, there is no cure and no one vaccine that covers all the various strains of meningococcal bacteria. Now, survivors and the relatives of victims are demanding immediate Federal Government action.

In this emotion-charged report, Tara Brown goes to New Zealand, where the Government has bitten the bullet and committed $200 million to the fight against meningococcal disease.

Back home, she confronts the Federal Health Minister Kay Patterson, who says the Government is studying the problem but can't commit any funds just yet. That prompts the question — what price a life?

To read a **transcript** of this story click here.

# Pneumococcal: the deadly bug that can pop up anywhere

Jenna Price

## That's why there's a push to get the life-saving vaccine on the free list

PATRICK MOORE has a vivid recollection of a patient of his in Tamworth.

The child was perfectly healthy, primary-school age, went to bed feeling slightly unwell, maybe just a small headache. By the time morning came, he was brain-dead.

That would have been a productive life, says Moore, a Canberra pediatrician.

The boy died from the complications of pneumococcal disease.

Never heard of pneumococcal? In Canberra alone, there were 30 reported cases in 2002 and 19 of those were children under five.

It's a notifiable disease, but the bacterium which causes it can pop up in the kinds of infections that no-one would ever bother notifying. It's the kind of bug that risk groups such as Down syndrome and cystic fibrosis, but the majority of Australian parents would have to pay for it themselves.

There is no question that the vaccine, Prevnar, is expensive. By the time it makes its way to the retail outlet where ordinary consumers can buy it to take to their doctors for administration, the cost will be close to $500 for each patient. That covers the three doses needed for Prevnar to be fully effective.

In comparison, one of the last major vaccines to be added to the schedule for children under five was Hib vaccine — to prevent meningitis and epiglottitis — was just $40 for four doses in 1993 prices.

So, yes, Prevnar is expensive, but then, say doctors, so is the cost of looking after patients stricken with the disease.

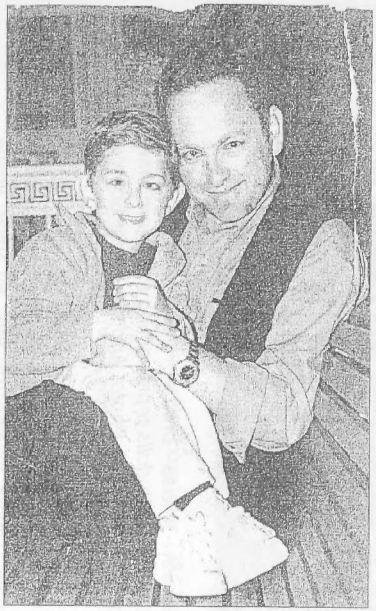
Paul Dugdale, chief health officer of the ACT, is puzzled by the Feceral Government's decision, particularly since the vaccine against meningococcal disease was approved as part of the free immunisation schedule last year.

Invasive Pneumococcal Disease is more common and causes more deaths than Invasive Meningococcal Disease, he says.

Dugdale sits on the National Health and Medical Research Council which publishes the Australian Standard Vaccination Schedule.

The most recent schedule recommended several vaccines which are not publicly funded, including one preventing the common childhood illness chicken pox.

While most children survive chicken pox unharmed, seven a year die from it and others suffer a variety of disfigurements



Dan Szabo with his son Jordan, 4. By the time the family knew what was the matter with their first-born, it was too late to prevent neurological damage.

like a bad cold, doctors there were puzzled by his symptoms.

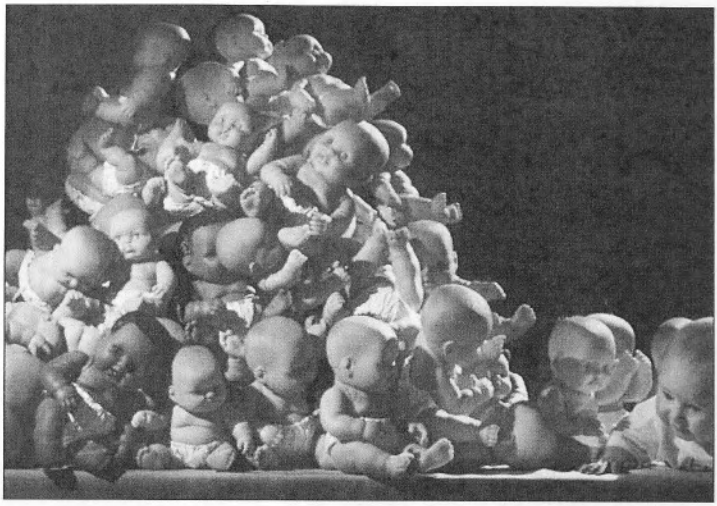
It's a common story with pneumococcal disease. It can be hard to pin down, especially since the patient is usually too young to be able to say what is troubling them. All doctors can see is an infant with a high temperature.

By the time the Szabos, who left Palmer-

says.

As Lana Atkinson, whose son Noah was admitted to Canberra with pneumococcal this week, says, "What does it cost to have my son and me in hospital for a week or more as public patients?"

Margaret Burgess, director of the National Centre for Immunisation



*Five-month-old Brandan Rudnick whose brother, Nathan died from pneumococcal disease in 1999 poses with dolls representing the [more than] 2000 children affected annually by the disease Photo: Andrew Taylor Source: The Age*

**Question 20: From a decision-maker/policy perspective, how do these media portrayals influence the debate over which vaccination program to fund? After seeing these articles, what other factors would you include in your list of criteria which influence whether or not a vaccine is publicly funded? Would you change your basic recommendation to your boss based on any of this information you have just considered? (5 minutes)**

# Conclusion:

While implementing a vaccination or similar program may involve more than just health and epidemiological considerations, it also goes beyond the 'money matters' which were the focus of this Lessons from the Field. At the end of the day, that political and social contexts within which a program is being considered are crucial to the final decision especially when Governments have ample health budgets with which to work.

Consequently, both vaccination programs were funded:

- In 2003, the MCCV was funded for all children at 12 months plus a catch up program for all who were born after 1984 (i.e., 119 year olds).
- In 2005, the 7vPCV was funded for all infants (2, 4, 6 months).

**Other resources:**


- World Health Organization (WHO). Making choices in health: WHO guide to cost-effectiveness analysis 2003 [cited 2013 April 20]: Available from: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf.
- Owens D. Interpretation of cost-effectiveness analysis. J Gen Intern Med. 1998;13(10):716-7.
- Scuffham P, Lowin A, Burgess M. The cost-effectiveness of varicella vaccine programs for Australia. Vaccine. 1999;18(5-6):407-15.
- Ray G. Pneumococcal conjugate vaccine: review of cost-effectiveness studies in Australia, North America and Europe. Expert Rev Pharmacoeconomics Outcomes Res. 2008. 2013 April 20;8(4):373-93.

# PART TWO

# EPI INFO™ 7 TRAINING SESSION WORKSHOP

Australian National University

# Introduction to Epi Info™ 7 Training Session

## Instructor Guide

This session was created based on a workshop designed by Stephanie Davis in May 2012. It is adapted from the Epi Info™ 7 Quick Start Guide and based on a session originally designed by Dr Kamalini Lokugue.

The dataset used in this session has been obtained from Epi Info™ 7 training material available from the US CDC.

Learning objectives:

- Describe the major uses of Epi Info™ 7
- Use Epi Info™ 7 to:
  - Develop questionnaires, enter data and create cluster maps
  - Transfer data into and out from Epi Info™ 7
  - Perform basic analysis using the Visual Dashboard Tool for descriptive statistics, recoding of variables, creating graphs and 2x2 tables to calculate measures of association
  - List the advantages and disadvantages of analysing data in the Epi Info™ 7 Classic Analysis Tool versus the Visual Dashboard Tool
  - Understand the range of statistical tests offered by StatCalc

## TOPIC 1: Welcome to the Introduction to Epi Info™ 7 Training Session (10 minutes)

*Welcome students to the session. Introduce the instructors and get students to briefly introduce themselves, including their background, why they are attending this session and what they hope to get out of it. Any logistical information required by students to be included in this Topic.*

## TOPIC 2: Introduction to the Training Session and Epi Info™ 7 (1015 minutes)

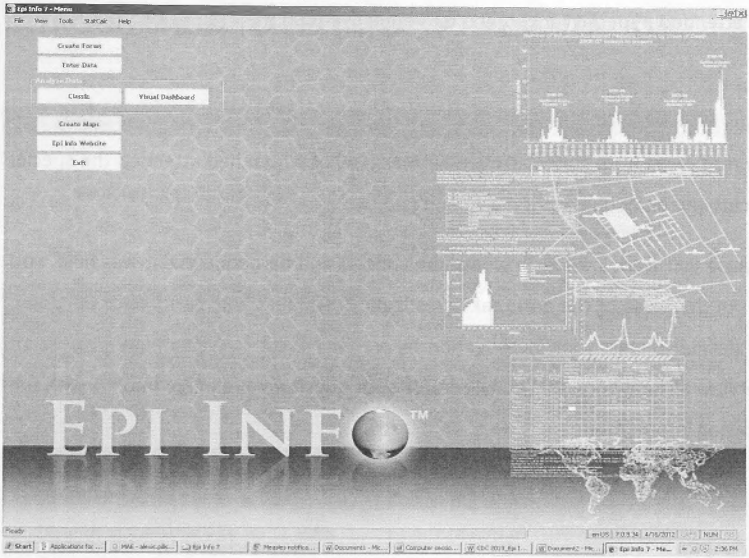
The instructor will give a Powerpoint presentation providing:

- An overview of the learning and course objectives for this session;
- The format for the session;
- An overview of Epi Info™ 7 and its uses and capabilities.

*After Powerpoint presentation, instructor to launch Epi Info and ensure all students have successfully done so.*

To launch Epi Info™ 7:

- Double click the Epi Info icon on your desktop.
- Click on the Launch Epi Info button. This should bring up the main menu screen for Epi Info.




## TOPIC 3: Questionnaire development and mapping

*Instructor to introduce case study for the questionnaire and mapping section.*

**Case study**

You are a newly employed epidemiologist at the Bavarian state health department in Munich, Germany. You are contacted by a local hospital on Wednesday, July 18 and informed that there have been multiple reported cases of Shiga-toxin producing *E. coli* (STEC). After preliminary interviews with several known cases, you discover that all cases are members of Germany's David Hasselhoff Fan Club who

had attended a special concert and barbeque event on the evening of Saturday, July 14.

It quickly becomes apparent that this outbreak has been extensive, with 359 reported cases from states all over Germany, all of whom had attended the special concert and barbeque event.

Because you work in Munich where the concert and barbeque event was held, you are put in charge of the outbreak investigation. To identify the source of infection, you decide to start your investigation by creating a Food Questionnaire to use to interview all known cases. You will create your questionnaire in Epi Info™ 7 with the following information:

- Case ID
- Demographic details
  - First name
  - Last name
  - Date of birth
  - Age
  - Sex
  - Address
- Clinical details:
  - Date of onset of symptoms
  - Headache (yes/no)
  - Fever (yes/no)
  - Bloody diarrhoea (yes/no)
- Food history 210 days before onset of symptoms:
  - Sour cream
  - Beansprouts
  - Beef jerky

# INTRODUCTION TO EPI INFO™ 7 PRESENTATION

Introduction to Epi Info™ 7

Topics 1 & 2: Welcome and Introduction

19 March 2013
CDC Conference

## Topic 2: Outline

- Learning & course objectives
- Course agenda
- Explanation of course materials & instruction methods
- Quick overview of Epi Info™ 7
- Downloading & installing Epi Info™ 7

## Learning objectives of this course

- To provide an introduction to Epi Info™ 7 and its capabilities in the management, manipulation, display & analysis of data
- To provide an overview of and experience with Epi Info™ 7's most commonly used functions:
  - Electronic form creation & data entry
  - Mapping and visualisation
  - Basic statistical analysis & data management

## Course objectives

- After completing training participants will be able to:
  - Develop questionnaires, enter data & create cluster maps
  - Transfer data into & out of Epi Info
  - Perform basic analysis using the Visual Dashboard Tool for descriptive statistics, recoding of variables, creating graphs && 2x2 tables to calculate measures of association
  - List the advantages & disadvantages of analysing data in the Epi Info™ 7 Classic Analysis Tool versus the Visual Dashboard Tool
  - Understand the range of statistical tests offered by StatCalc

## Course agenda

1. Welcome & introductions
2. Introduction to training course & Epi Info™ 7 overview
3. Questionnaire & mapping
4. Overview of data analysis
5. Data analysis using Visual Dashboard
6. Classic Analysis
7. StatCalc
8. Summary & conclusion

## Explanation of course materials & instruction methods

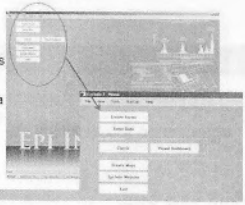
- Course material handouts
- Instruction methods:
  - This is an introductory training session.
  - This session assumes basic knowledge of epidemiology & statistics.
  - This session is not an introduction to statistical analysis.
  - Students will be exposed to a broad overview of Epi Info™ 7 features & functions.
- Instructional format for each Topic:
  - PowerPoint Presentation
  - Demonstration
  - Practice

## Quick overview of Epi Info™ 7

- Public domain suite of software tools designed for global community of public health practitioners by the US CDC
- Free to download, use & distribute
- Features include:
  - Rapid electronic Form creation & data entry
  - Statistical analysis
  - Mapping & visualisation

## Epi Info™ 7 main menu

- Create Forms
- Enter Data
- Analyse Data
- Create Maps
- StatCalc



## Create Forms

- Create electronic data entry Forms. Templates are available or can be custom designed. Forms can be designed to include automatic calculations, skip patterns, etc.

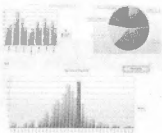
## Enter Data

- Used to collect data into the Form. Addresses can be geocoded into latitude & longitude.

## Maps

- Uses longitudinal/latitudinal data to create case cluster or choropleth maps.

## Visual Dashboard



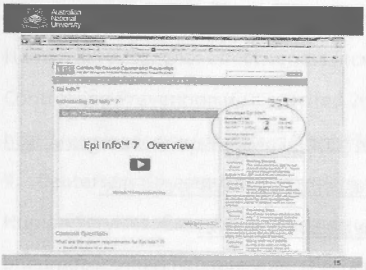
- Quick analysis. Can run statistical tests, generate tables, graphs, charts, recode variables. Output is saved as a Canvas or HTML file.

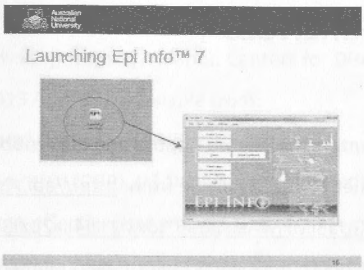
## StatCalc

- Basic Statistical Calculator. Can perform analyses of single or stratified two-by-two tables, determine sample size for studies, etc.

## Downloading and installing Epi Info™ 7

- Epi Info™ 7 program files can be accessed at http://www.cdc.gov/epiinfo/7/index.htm
- Setup Installation (.exe file)
  - Traditional way of installing Windows applications
  - Requires administrator privileges to run
- Zip File Deployment (.zip file)
  - Compressed "zip" archive
  - Does not require administrator privileges to run


Epi Info™ 7 Overview


Launching Epi Info™ 7
EPI INFO

# REFERENCES


1. Centers for Disease Control and Prevention (CDC). EpiInfo 7 quick start guide [Internet ] 2012. Available from: http://api.ning.com/files/i4WR*oy5zFtRk-PmzgGUa8iMkIwAkbQbu6*IdxSl2slg4La2bZl3wXJb50nY7g6OVc-1jF4TNbpQ7OrpGqk6DRY5jFgOGcSF/EpiInfo7QuickStartGuide_020.pdf.
2. Collins H. Links for Epi Info training slides. 2012 [cited 2013 April ]; Available from: http://www.phconnect.org/group/epiinfo/forum/topics/links-for-epi-info-training-slides?commentId=3649725%3AComment%3A95737&groupId=3649725%3AGroup%3A3293.
3. Australian Government Department of Health and Ageing. Immunisation advisory bodies. [Internet]. 2013 [updated 2013 April 18; cited 2013 April 19]; Available from: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/advisory-bodies.
4. Roche P, Krause V. Invasive pneumococcal disease in Australia, 2001. Communicable Diseases Intelligence. 2002;26(4):505-519.
5. Centers for Disease Control and Prevention (CDC), US Department of Health & Human Services. Introduction to economic evaluation. [Internet]. Atlanta: Centers for Disease Control and Prevention (CDC); [cited 2013 April 12]; Available from: http://www.cdc.gov/owcd/eet/SeriesIntroduction/TOC.html.
6. World Health Organization (WHO). The global burden of disease: 2004 update. Geneva: World Health Organization 2004.
7. Centers for Disease Control and Prevention (CDC), US Department of Health & Human Services. Framing an economic evaluation. [Internet]. Atlanta: Centers for Disease Control and Prevention (CDC); [cited 2013 April 12]; Available from: http://www.cdc.gov/owcd/eet/Framing3/1.html.

8. Centers for Disease Control and Prevention (CDC), US Department of Health & Human Services. Cost effectiveness analysis. [Internet]. Atlanta: Centers for Disease Control and Prevention (CDC); [cited 2013 April 12]; Available from: http://www.cdc.gov/owcd/eet/CostEffect2/1.html.

9. Centers for Disease Control and Prevention (CDC), US Department of Health & Human Services. Case study: applying cost-effectiveness analysis to a pneumococcal-conjugate vaccination program. [Internet]. Atlanta: Centers for Disease Control and Prevention (CDC); [cited 2013 April 12]; Available from: http://www.cdc.gov/owcd/eet/PneuVaccCEA/1.html.

10. World Health Organization (WHO). CHOosing Interventions that are Cost Effective (WHO-CHOICE). [Internet]. Geneva: World Health Organization (WHO); 2013 [cited 2013 April 12]; Available from: http://www.who.int/choice/en/.

# APPENDICES

## Appendix 7.A. Answer guide for Lessons from the Field

Question 1

**Which type of economic evaluation do you think would be the most appropriate for deciding whether to fund the 7vPCV vaccine and why?**

Good student answer

- *Cost effectiveness analysis*
  - *The analysis needs to incorporate the measure of health outcomes, which can be a single dimensional measure such as incidence, death, hospitalisations etc.*
  - *CA therefore is not appropriate. So is CBA as measuring health outcomes in monetary terms in this context will be problematic.*
  - *CUA can be considered to take into account of QALY/DALY but this usually done when QOL is the important outcome, for e.g. chronic diseases*
- *In public health we try to do the greatest good for the greatest number of people. The purpose of a vaccine is to prevent or modify disease. The Cost-Effective evaluation is the most appropriate as it compares the cost of the intervention to the potential health gains, usually in cases prevented.*

Other points to consider

- You could argue for more than one choice (though not for a basic cost analysis).
- Think about what kind of information we want and who wants it – what is the decision level? E.g, a high ranking government official is only going to care about the bottom line in dollars and not about quality of life interpretations for individuals affected by funding a program/intervention.

- A cost-effectiveness analysis would allow you to calculate a cost in $ value per health outcome achieved which is a useful measure for a body like ATAGI to consider. It is easier to absorb than a summary measure from a cost-utility analysis but provides more detail than the single dollar value determined from the summary measure in a cost-benefit analysis.

**Question 2**

**What is the study problem? (I.e., what question are you trying to answer?)**

Good student answer

- Should 7vPCV be universally funded for infants < 12 months of age?

Other points to consider

- A more thorough economic evaluation question would be: what are the incremental costs as measured in terms of IPD disease and deaths averted of implementing a new universal infant pneumococcal vaccination program?

**Question 3**

**Why is this problem important? What aspects of the problem do you need to understand in order to grasp its importance in light of the Government's decision on whether or not to fund the vaccine program?**

Good student answer

- *... consideration needs to made as to where this money can be used most effectively to improve population health as well as take into account other*

*considerations such as public interest and if there are other interventions/programs that will achieve similar outcomes.*

- *The problem is important as it can cause severe disability and even death and affects the most vulnerable individuals...We need understand the burden of disease and consider the economic impact of the disease on society...*
- *-Level of preventability*

  *-The costs of disease to society as a whole and also the cost of inaction. Other important aspects that need to be considered include access to the vaccine, the cost of the vaccine, the cost of administering the vaccine and the efficacy of the vaccine. It's also important to understand that the 7vPCV has been demonstrated to have a population effect, so by vaccinating the <2yrs, thereby doing the greatest good for the greatest number of people.*

Other points to consider

- How much will this program cost and where is that money coming from?
- Will any programs be cut to fund this program and if so what?
- Will we require any catch up campaigns or will any other age groups require vaccination? How much would these programs cost?
- Are there any adverse events associated with the vaccine?
- How many doses does this vaccine require? What would be the timing associated with the doses?
- What is the estimated herd immunity associated with this vaccination and could that impact its costs over time?

**Question 4**

**What is/are the alternative intervention(s)? What characteristics of the alternatives would be useful for you to understand in order make a comparison with the proposed program?**

Good student answer

- *The alternatives are to maintain status quo and continue to fund only for Indigenous and high-risk infants, consider other primary prevention strategies addressing the risk factors for IPD, or focus efforts of secondary or tertiary level prevention. We need to compare the effectiveness of these alternatives, their scope of effect (i.e. individual or population), and feasibility.*
- *The alternative intervention is treating cases as they occur. To compare this to a vaccination, it's useful to know hospital admission costs associated with the disease as well as the costs of medication, administration costs associated with hospital admission and productivity losses associated with carers lost wages. It's also important to understand that death is not reversible and the illness can result in disability that is life-long. It would be useful to know what the cost associated with disability is over the life-span of a person.*

Other points to consider

- Basically, we are comparing implementing this new vaccine program against no program because there hasn't been a universal program. We therefore need to understand the costs associated with doing nothing as compared with implementing this program.
- Considering programs targeting subgroups (like the one targeting Indigenous and high-risk infants) or other non-vaccination based programs could also be appropriate. (These haven't been factored into this session, however.)

**Question 5**

**Who is the audience for this study? (I.e., who is interested in or will use the results?)**

Good student answer

- *-Policy makers & those financing the system - government*
  *-Drug companies supplying vaccine (cha ching!)*
- *-Key decision makers at both federal and state departments. This includes ATAGI, PBAC, NCIRS*

Other points to consider

- Your audience is really only those who will use the results of your study to make decisions. Therefore, your primary audience will be the Government who need to decide whether or not to fund this vaccination program. ATAGI may also be interested (and maybe PBAC though they would do their own proper analysis).
- You could argue that healthcare providers and the public would have an interest in the results but they wouldn't be your main audience.

**Question 6**

**What is the study perspective? (I.e., from whose viewpoint is the study being conducted?)**

Good student answer

- *The provider perspective as we are looking at the costs of the program which will be funded by the government if it is approved.*

Other points to consider

- The perspective is the viewpoint from which the study is being conducted. It takes into account those who pay for the program costs and are affected by

the outcomes. Determining this helps determine which costs and outcomes are relevant and need to be included in your study. The perspective for your study would be the provider perspective – i.e., the Australian Government. You could also conduct the study from the societal perspective which would consider all costs and outcomes.

Question 7

**What would be a realistic timeframe for the study? (I.e., what is the period of time during which the program/intervention will be implemented?)**

Good student answer

- *It would have to be > 6 months (the time it would take for a 3-dose schedule to be complete). At least 1–2 years would need to be required to at least have one full cohort and also account for initial 'teething' where uptake of the vaccine may be low.*

Other points to consider

- The timeframe is the period during which the intervention is delivered.
- One year would give you enough time to see an annual cohort of infants receive the complete dose regimen.

Question 8

**What is the study's analytic horizon? (I.e., what is the entire period during which costs and benefits related to the impact of the program/intervention will be measured?)**

Good student answer

- *The analytic horizon will be the length of follow up required after the implementation of program to observe measurable changes in health outcomes.* (A great vague, diplomatic answer!)

Other points to consider

- This is a difficult question to answer and all students included good components to consider, like whether the vaccine confers long-term cross-protection of other strains of *S. pneumoniae*, whether we know how long the vaccine is effective for, whether we know anything about herd immunity effects.
- You could assume that the vaccine would prevent pneumococcal disease until a child was five years old and therefore that the analytic horizon should be five years. This may be conservative.

**Question 9**

**What do you think would be the most appropriate/realistic study format to use for this evaluation? (I.e., how will you assess the program/intervention?)**

Good student answer

- *Modelling is the most realistic and time/labour effective option... but will also require some assumptions, thus validity may be an issue.*
- *If funding is available, the most appropriate study would be a prospective study as data collected would be more reliable than retrospective and modelling which uses a number of assumptions.*
- *A combined study design incorporating retrospective study for baseline data and prospective study for follow up of health outcomes, using a series of administrative datasets.*

Other points to consider

- A prospective study considering a representative sample of an annual birth cohort would be the best option but it would be time and resource intensive. Modelling could be considered using decision-analysis software if the resources do not exist for a prospective study. We would need appropriate software and expertise for this. Both study types could be considered.

**Question 10**

**What costs do you think should be included in the analysis?**

Good student answer

- *-Direct medical: hospital costs (in-patient, out-patient, ED), general practice costs, medications and diagnostic costs.*

  *-Direct non-medical cost: loss of productivity of parents/patient, administration (healthcare facilities and Medicare)*

  *-Cost of vaccine and cost to roll-out the program (media campaigns, administration, staff, logistics etc.)*

Other points to consider

- We need to include program costs, direct costs (medical and nonmedical) and productivity losses. We should do this for both no vaccination program and for the program in order to compare.
- Program costs= cost of vaccine and administrative costs per dose

- Medical costs could include hospitalisation costs, emergency room costs, diagnostic test costs, surgery costs, prescription drug costs, outpatient costs, etc. We could break these down further.
- Nonmedical costs could include administrative costs and parent/caregiver lost time from work.
- Productivity losses would be those of the child. This is difficult to assess and would involve questionnaires aimed at understanding quality of life based on parent or caregiver answers. If we are conducting the evaluation from the provider/payer perspective, we do not need to include productivity losses.

**Question 11**

**What would be the intermediate and final outcome measures in your evaluation?**

Good student answer

- *-Intermediate outcomes:*

  *Number of vaccines given*

  *Vaccine uptake*

  *-Final outcome:*

  *Incidence of disease (based on notifications, hospitalisations) and complications*

  *Deaths from disease*

Other points to consider

- Outcome measures are units used to assess the output of the program or intervention.

- Though using final outcomes may be preferred, intermediate outcomes are often used because they are available and the final outcome data are insufficient. Moreover, intermediate outcomes may be used if a strong causal link exists between the intermediate and final outcomes.
- For this study, the intermediate outcome could include the number of children vaccinated. The final outcomes would be a better indicator of the effectiveness of the program and could include the numbers of meningitis or bacteraemia, pneumococcal pneumonia, otitis media, infection, disability or death.

**Question 12**

**What will be the final summary measure in this evaluation?**

Good student answer

- *Cost-effectiveness ratio*

Other points to consider

- Cost-effectiveness ratio= net costs/cases prevented (or another natural health unit like deaths prevented)

**Question 13**

**What are the anticipated program costs based on the estimations in the table above?**

Good student answer

- *Cost of vaccination:*

  *Total vaccination cost (for each child x 3 doses) = $270.00x250,000=* ***$67.5m***

*Total administration cost (for each child x 3 doses) = $15.00x250,000=* ***$3.75m***

***= $71.25m***

Question 14

**What is the net cost of implementing this program?**

Good student answer

- *Total program costs (from above):* ***$71.25 million***

  *Total program costs =*

  *Total treatment costs - no vaccination program =* ***$144.2 million***

  *Total treatment costs - with vaccination program =* ***$127.3 million***

  *Difference in treatment costs between no vaccination and implementing the vaccination program =* ***$16.9 million***

  *Total costs of implementing this vaccination program =*

  *Net cost = Program costs – disease costs averted =*

  ***$71.25 million – 16.9 million = $54.35 million***

Question 15

**How many health outcomes would be prevented by the vaccination program?**

Good student answer

- *552 cases of disease and 12.4 deaths would be averted by implementing the vaccination program*

**Question 16**

**Calculate the CER in terms of cost per case of disease prevented and cost per death averted. Interpret these results – what do they mean?**

Good student answer

- *All were correct*

  *54.35 m / 552 cases prevented = $98,460*

  *54.35 m / 12.4 deaths prevented = $4,383,064*

Other points to consider

- This program costs $54.34 million and results in 552 cases prevented and 12.4 deaths averted. With the program, each additional case averted costs $98,460 and each additional death averted costs $4.83 million.
- This ratio would allow us to compare the program with other vaccination programs.

**Question 17**

**Is this an expensive vaccine program? What is your instinctive opinion (and basic recommendation to your boss) on whether it is cost-effective or not?**

Good student answer

- *It seems like a very expensive program and my instinctive opinion would be not to support the program. Having said that however I'd like to do more research comparing this against a cost effective analysis of vaccinating 'at risk' children and Aboriginal and Torres Strait Islander people only. I'd also like to compare it against the CEA's of other vaccination programs that have been included and excluded from the immunisation schedule.*
- *I don't know if this is expensive, I'd need to refer to other programs to gauge the expense. But what value do you put on a life? My instinct indicates this is not expensive, especially when productivity losses and intangible losses are not included in the analysis.*

Other points to consider

- It would appear that this is an expensive program but we'd need to have other programs' CERs calculated in order to make a comparison. For example, a study on the cost-effectiveness of varicella vaccination determined that the vaccine cost $64 to prevent one case of chickenpox. Clearly, comparing the two, the pneumococcal program is dramatically more expensive.
- Answering this question requires us to ask whether or not this is good value for money – and this is a value judgement. What is the threshold which we apply that determines this depends on who the decision-maker is, how the decision-maker values health outcomes and money, how willing the decision-maker is to substitute one for the other, and the decision-maker's attitude towards risk. If the decision-maker is the Government, then general societal consensus will also influence the decision. The resources available will also contribute to this decision.
- A cost-effectiveness evaluation is subjective and is meant to provide a general guideline as to whether a program is reasonably efficient, questionably efficient or inefficient.

Question 18

**What other parameters should be subjected to sensitivity analyses?**

Good student answer

- *-Vaccine efficacy*
  *-Discount rate*
  *-Positive effects of herd immunity*
- *-Cost of vaccine*
  *-Cost of health services*

Other points to consider

- Other factors which could impact on the study results should be subjected to sensitivity analyses. These could include vaccine efficacy, incidence of pneumococcal disease, treatment costs (which could be broken down more thoroughly), vaccine administration cost, cost of the vaccine, discount rates.
- A range of possible values should then be employed and results recalculated accordingly. If the study results change significantly and have therefore reacted very sensitively to a particular set of parameters, then results should be interpreted carefully.

Question 19

**Roughly, how does this compare with what you worked out for the cost-effectiveness of the 7vPCV program? What would your recommendations to your boss be in terms of which vaccine to fund? What types of information would help you to better make your recommendation?**

Good student answer

- *I'd recommend funding the MCCV program over the IPD program as the MCCV program is a lot more cost effective than the 7vPCV program particularly cost per death.*

  *Types of information to help make recommendations:*

  *-CEA of the 'high risk' vaccination program for IPD*

  *-Efficacy, duration of efficacy and adverse events of both meningococcal C and 7vPCV vaccines,*

  *-Public interest*

  *-CEA comparison with other vaccines on the immunisation schedule and vaccines that did not make it onto the schedule*

- *The 7vPCV is a bit more expensive than the meningococcal C vaccine. I see where you're going in terms of cheaper cost vs. more of the population covered but I couldn't choose, it's not ethical as you're talking about the lives of children. I'd tell him to fund both. In terms of outcomes, they can both be just as devastating. Maybe I'm just not meant to be one of those people that have to make these decisions.*

Other points to consider

Pneumococcal:

54.35 m / 552 cases prevented = $98,460

54.35 m / 12.4 deaths prevented = $4,383,064

Meningococcal:

9.6m / 130 cases prevented = $73,846

9.6 m / 13 deaths prevented = $738,462

- The pneumococcal program is significantly more expensive to fund at 54.35 million compared with the meningococcal program. It is cheaper to prevent a case of meningococcal or a death from meningococcal than it is pneumococcal. The meningococcal program is also expensive however.
- Notification rates and mortality rates are both higher for invasive pneumococcal as is the impact from non-invasive pneumococcal disease states.
- Based on this rough data, and understanding that both are expensive, you could consider recommending funding the pneumococcal program because it is has the potential to avert more disease burden. It is not always better to fund the cheaper program. This is absolutely subjective and there is no right answer for this question.
- We would want to know how these costs compare with other vaccine programs, whether a catch up campaign would be necessary, and if so how extensive would that be and how costly? How long do the vaccines last for? Where would the funding come for either program? Are both vaccines equally effective and equally effective for invasive disease, non-invasive disease and long term sequelae? Are they both effective for all serotypes of the disease? Do we have enough to fund each? Do we have enough money to fund both?
- Also, knowing that there is already a PCV program in place for Indigenous and high-risk infants, we'd want to know what proportion of the age cohort is covered by this program.

Question 20

**From a decision-maker/policy perspective, how do these media portrayals influence the debate over which vaccination program to fund? After seeing these articles, what other factors would you include on your list of criteria which influence whether or not a vaccine is publicly funded? Would you change your basic recommendation to your boss based on any of this information you have just considered?**

Good student answer

- *The media portrayed both diseases as sudden and deadly diseases that affects mostly children and are incurable. They framed the diseases in a highly emotive manner (for e.g. 'what price is life?') and alleged that the government is doing nothing about this. This will influence the debate significantly because we are dealing with a group of vulnerable populations and the government would always want to give the image that they are doing something and are responding to the public's concerns.*

  *Other factors to consider are the societal perspective and the potential public backlash of not funding a potentially preventable disease.*

  *I would incorporate this issue into my recommendation and have a measured approach that considers not only the epidemiological and economics aspects of the disease but also the political and social dimensions of this.*

Other points to consider

- Beyond just burden of disease, vaccine characteristics, immunisation strategy and cost-effectiveness, other factors come into play with funding a vaccine, including the program's acceptability and equity, as well as ethical, legal and political considerations.

- While implementing a vaccination or similar program may involve more than just health and epidemiological considerations, it goes beyond the 'money matters' which were the focus of this Lessons from the Field. At the end of the day, the political and social context within which a program is being considered is crucial to the final decision, especially when countries have substantial health budgets to work with.
- Consequently, both of these vaccination programs were in fact funded.

## Appendix 7.B. Schedule for Epi Info™ 7 training session

| Topic | Format | Time (pm) |
|---|---|---|
| Topic 1: Welcome and introduction<br>Introduction – staff and participants<br><br>Logistics | Round table | 1.30 – 1.40<br>Alexis |
| Topic 2: Introduction to Epi Info and the training session<br><br>• Learning objectives<br>• Epi Info Overview<br>• Capabilities and uses<br>• Format of session | Power point presentation | 1.40 – 1.55<br>Alexis |
| Introduction to case study | Power point presentation | 1.55 – 2.00<br>Alexis |
| Topic 3: Questionnaire and maps<br><br>• Learning objectives<br>• Introduction to questionnaires and maps<br>• Create form<br>• Enter data<br>• Create a cluster map | Power point presentation<br><br>Instruction demonstration<br><br>Participant activities | 2.00 – 3.00<br>May<br>Rowena |
| Break for 15 minutes | | |
| **Topic** | **Format** | **Time (pm)** |
| Topic 4: Overview of data analysis<br>Classic and visual dashboard | Power point presentation | 3.15 – 3.20<br>Ranil |
| Topic 5: Data analysis using visual dashboard<br><br>• Learning objectives<br>• Data import / export, open Epi Info dataset<br>• Descriptive statistics<br>• Frequency tables, summary statistics<br>• Recode variables<br>• Create graphs / epi curve<br>• 2x2 tables | Instruction demonstration<br>Participant activities | 3.20 – 4.15<br>Ranil |

| Topic | Format | Time (pm) |
|---|---|---|
| Topic 6: Classic analysis | Instruction demonstration | 4.15 – 4.30 Ee Laine |
| Topic 7: Stat calc<br>• Introduce the range of statistical functions and when to use them<br>• Use stat calc to assess if ↑ cases occur by chance | Power point presentation<br>Instruction demonstration<br>Participant activities | 4.30 – 4.45 Ee Laine |
| Summing up discussions and final questions<br><br>Evaluation forms | Instructor leads discussion | 4.45 – 5.00 Ee Laine |

## Appendix 7.C. Results from the Epi Info™ 7 training session evaluation

At the completion of the Epi Info™ 7 teaching exercise, an evaluation form (Appendix 7.E) was handed out to all the participants. Ten responses were received. The responses to the questions in the evaluation forms appear below:

1. ***How well organized was the Epi Info™ 7 course?***

Two of the ten participants (20%) stated it was "extremely organized", eight (80%) stated it was "very organized" and 1 participant (10%) stated it was "moderately organized".

2. ***Had you used Epi Info™ before this session (you can tick more than one box)?***

Three participants (30%) answered "Yes - a bit", two participants (20%) answered "Yes - but a long time ago", 4 participants (40%) answered "no" and one participant (10%) answered "Yes – but a long time ago" and "Yes- but an older version"

3. ***How useful to your job was the information presented at the Epi Info™ 7 course?***

Six participants (60%) answered that it was "very useful" and four participants (40%) answered that it was "moderately useful".

4. ***How much have your skills improved because of training at the course?***

One participant (10%) answered " a great deal", four participants answered "a lot" and four participants (40%) answered a moderate amount. One participant did not answer the question.

5. ***How comfortable did you feel asking questions at the course?***

Two participants (20%) answered "extremely comfortable" and eight participants (80%) answered "very comfortable".

6. ***How friendly were the presenters?***

Five participants (50%) answered "extremely friendly" and five participants (50%) answered "very friendly"

7. ***Did the presenters allow enough time for the computer exercise?***

Eight participants (80%) answered that it was "about the right amount", 1 participant (10%) answered that it was "slightly too little". One participant wrote: "varied sometimes too little, depended on program playing up"

8. ***How easy was it to keep up with the exercise?***

Two participants (20%) answered that it was "extremely easy", four participants (40 %) answered that it was "very easy", and four participants (40%) answered that it was "moderately easy".

9. ***What suggestions do you have for improving the Epi Info™ course if it were to be run again?***

Comments received were:

- "Larger screen, sometimes difficult to see what presenter was doing. If bringing laptop, more information on system requirements"
- "More exercises to work through"
- "Invite participants to bring current dataset under investigation"
- "Keep class size small"

**10. Overall, how satisfied were you with the Epi Info™ 7 course?**

Six participants (60%) answered that they were "extremely satisfied" and four participants (40%) answered that they were "moderately satisfied".

**11. If you have any comments about the Epi Info™ 7 course, please write them below:**

Comments received were:

- "Thank you...now I'll know where to start when that outbreak hits!!"
- "Good course materials"
- "Thanks for allowing this great opportunity. Cheers"

## Appendix 7.D. Evaluation of the Epi Info 7™ training session

This is a short evaluation of the Epi Info™ 7 course that was run on 18 March 2013. Thank you for taking the time to complete this form. The information will be used to improve future sessions.

1. How well organized was the Epi Info™ 7 course?

   - ☐ Extremely organized
   - ☐ Very organized
   - ☐ Moderately organized
   - ☐ Slightly organized
   - ☐ Not at all organized

2. How useful to your job was the information presented at the Epi Info™ 7 course?

   - ☐ Extremely useful
   - ☐ Very useful
   - ☐ Moderately useful
   - ☐ Slightly useful
   - ☐ Not at all useful
   - ☐ Other (please specify) _____

3. How much have your skills improved because of training at the course?

   - ☐ A great deal
   - ☐ A lot
   - ☐ A moderate amount
   - ☐ A little
   - ☐ None at all

4. How comfortable did you feel asking questions at the course?
   - ☐ Extremely comfortable
   - ☐ Very comfortable
   - ☐ Moderately comfortable
   - ☐ Slightly comfortable
   - ☐ Not at all comfortable

5. How friendly were the presenters?

   - ☐ Extremely friendly
   - ☐ Very friendly
   - ☐ Moderately friendly
   - ☐ Slightly friendly
   - ☐ Not at all friendly

6. Did the presenters allow enough time for the computer exercises?

   - ☐ Much too much
   - ☐ Somewhat too much
   - ☐ Slightly too much
   - ☐ About the right amount
   - ☐ Slightly too little
   - ☐ Somewhat too little
   - ☐ Much too little

7. How easy was it to keep up with the exercises?

   - ☐ Extremely easy
   - ☐ Very easy
   - ☐ Moderately easy
   - ☐ Slightly easy
   - ☐ Not at all easy

8. What suggestions do you have for improving this Epi Info™ course if it were to be run again?

9. Overall, how satisfied were you with the Epi Info™ 7 course?

- ☐ Extremely satisfied
- ☐ Moderately satisfied
- ☐ Slightly satisfied
- ☐ Neither satisfied or dissatisfied
- ☐ Slightly dissatisfied
- ☐ Moderately dissatisfied
- ☐ Extremely dissatisfied

10. If you have any comments about the Epi Info™ 7 course, please write them below:

**THANK YOU FOR COMPLETING THIS EVALUATION!!**